

The CAPTURE Study: Validating a unique COPD case finding tool in primary care

Protocol Number: 1R01HL136682

National Clinical Trial (NCT) Identified Number:

NCT03581227, NCT03653611, NCT03583099

Principal Investigators:

Fernando J. Martinez, M.D., Weill Cornell Medicine

MeiLan K. Han, M.D., University of Michigan

Funder:

National Heart, Lung, and Blood Institute (NHLBI)

Version Number: v. 8.0

17 July 2023

| Protocol Amendment 8.0 - Summary of Changes | | | | |
|---|-------------|----------------|--|--|
| Location | Page Number | Type of Change | Description | Rationale |
| Cover page | --- | Administrative | Update Protocol Version to 8.0 and update version date to 17JUL2023 | Amendment version and date |
| 1.1 Synopsis | 7 | Clarification | <p>Secondary Endpoints</p> <ul style="list-style-type: none"> • Aim 3 – <u>O</u> All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) Mild COPD 4) preserved ratio, impaired spirometry (PRISM), and 5) symptomatic non-obstructed (SNO) | Clarification of the secondary endpoints and what participants will be analyzed. |
| 1.3 Schedule of Assessments | 11,12 | Edit | <p>Footnote 3:</p> <p>3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score > 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as post-bronchodilator FEV1/FVC < 0.70 or FEV1 < 80% predicted at baseline, or pre-bronchodilator FEV1/FVC < 0.65 or FEV1 < 70% predicted for patients who do not complete post-bronchodilator spirometry; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data. For participants meeting criterion 3 where all of the protocol specified 12-month assessments cannot be made, another participant will be selected at random to replace this participant.</p> | The footnotes were edited to delete comment on replacing control patients who did not have availability of follow up data. |
| 1.3 Schedule of Assessments | 11 | Addition | CAPTURE questions added to 12-month evaluations | CAPTURE item additional questionnaire is to be collected at the 12-Month visit. |

| | | | | |
|--|----|---------------|---|---|
| 3.0 Objectives and Endpoints | 21 | Clarification | Aim 3 Endpoints: All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) <u>Mild COPD</u> , 4) preserved ratio, impaired spirometry (PRISm), and 5 4) symptomatic non-obstructed (SNO). | Clarification of the secondary endpoints and what participants will be analyzed. |
| 5.1 Inclusion Criteria | 27 | Addition | <u>4. Able to read and speak English or Spanish.</u> | Study participants could complete the baseline visit and any required follow up in English or Spanish |
| 8.2 Longitudinal Follow-Up Assessments and Data Collection | 34 | Deletion | Data collected from medical record: Deleted “oral anti-inflammatory” medications Deleted * and footnote for * | This edit confirms that oral anti-inflammatory medications will not be collected during the 12-month chart review. |
| 8.2 Longitudinal Follow-Up Assessments and Data Collection | 35 | Edit | Data Collection by the COPD Foundation Deleted “oral anti-inflammatory” medications <u>Added- CAPTURE questions</u> <u>Added- CAPTURE Additional Items Questionnaire</u> Deleted * and footnote for * | Data collected by the COPD Foundation will now include CAPTURE Questions and CAPTURE Additional Item Questionnaire. |
| 9.3.2 Practice Behavior (Aim 3) | 47 | Addition | All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD, <u>Mild COPD</u> , PRISm, and symptomatic non-obstruction. | Secondary analyses include Mild COPD as reflected throughout the protocol. |

1 TABLE OF CONTENTS

| | |
|---|----|
| STATEMENT OF COMPLIANCE | 1 |
| Abbreviations | 1 |
| 1 PROTOCOL SUMMARY | 3 |
| 1.1 Synopsis | 3 |
| 1.2 Schema | 7 |
| Figure 1. Overall structure of aims | 7 |
| Figure 2. structure of aim 2 | 7 |
| 1.3 Schedule of Activities (SoA) | 9 |
| 2 INTRODUCTION | 10 |
| 2.1 Study Rationale | 10 |
| 2.2 Background | 12 |
| Aims 1 and 3 | 12 |
| 2.3 Risk/Benefit Assessment | 14 |
| 2.3.1 Known Potential Risks | 14 |
| 2.3.2 Known Potential Benefits | 15 |
| 2.3.3 Assessment of Potential Risks and Benefits | 15 |
| 3 OBJECTIVES AND ENDPOINTS | 15 |
| 4 STUDY DESIGN | 19 |
| 4.1 Overall Design | 19 |
| 4.2 Scientific Rationale for Study Design | 21 |
| 4.3 End of Study Definition | 23 |
| 5 STUDY POPULATION | 23 |
| 5.1 Inclusion Criteria | 23 |
| 5.2 Exclusion Criteria | 24 |
| 5.3 Screen Failures | 24 |
| 5.4 Strategies for Recruitment and Retention | 25 |
| 6 STUDY INTERVENTION | 25 |
| 6.1 Study Intervention(s) Administration | 25 |
| 6.1.1 Study Intervention Description | 26 |
| 6.2 Measures to Minimize Bias: Randomization and Blinding | 27 |
| 6.3 Study Intervention Compliance | 27 |
| 6.4 Concomitant Therapy | 28 |
| 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL | 28 |
| 7.1 Discontinuation of Study Intervention | 28 |
| 7.2 Participant Discontinuation/Withdrawal from the Study | 28 |
| 7.3 Lost to Follow-Up | 28 |
| 8 STUDY ASSESSMENTS AND PROCEDURES | 29 |
| 8.1 Baseline assessments and data collection | 29 |
| 8.2 Longitudinal follow-up assessments and data collection | 31 |
| 8.3 aim 2 assessments and data collection | 32 |
| 8.4 Adverse Events and Serious Adverse Events | 35 |
| 8.4.1 DEFINITION OF ADVERSE EVENTS (AE) | 35 |
| 8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE) | 35 |

| | | |
|--------|---|----|
| 8.4.3 | TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP | 37 |
| 8.4.4 | Adverse Event Reporting..... | 37 |
| 8.4.5 | Serious Adverse Event Reporting | 37 |
| 8.5 | Unanticipated Problems | 37 |
| 8.5.1 | Definition of Unanticipated Problems (UP)..... | 37 |
| 8.5.2 | Unanticipated Problem Reporting..... | 38 |
| 8.6 | Safety Oversight..... | 38 |
| 9 | STATISTICAL And analytical plans | 38 |
| 9.1 | Sample size and POWER | 38 |
| 9.2 | Populations for Analyses..... | 42 |
| 9.3 | Statistical Analyses | 42 |
| 9.3.1 | SENSITIVITY AND SPECIFICITY (Aim 1)..... | 42 |
| 9.3.2 | PRACTICE BEHAVIOR (Aim 3)..... | 43 |
| 9.3.3 | CAPTURE IMPLEMENTATION RECOMMENDATIONS (Aim 2)..... | 44 |
| 10 | SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS | 45 |
| 10.1 | Regulatory, Ethical, and Study Oversight Considerations..... | 45 |
| 10.1.1 | Informed Consent Process..... | 45 |
| 10.1.2 | Study Discontinuation and Closure | 46 |
| 10.1.3 | Confidentiality and Privacy | 46 |
| 11 | STUDY ADMINISTRATION AND OVERSIGHT | 47 |
| 11.1 | Study Leadership | 47 |
| 11.1.1 | Principal Investigators | 47 |
| 11.1.2 | practice based research networks (pbrn) | 47 |
| 11.1.3 | Spirometry Core | 48 |
| 11.1.4 | Implementation core | 49 |
| 11.1.5 | Data coordinating center (DCC)..... | 49 |
| 11.1.6 | Clinical Coordinating Center..... | 49 |
| 11.1.7 | 12 month survey Coordinating Center..... | 51 |
| 11.2 | Organizational Structure..... | 51 |
| 12 | Quality Assurance and Quality Control | 52 |
| 13 | Data Handling and Record Keeping..... | 52 |
| 13.1 | Data Collection and Management Responsibilities | 53 |
| 13.2 | Study Records Retention | 53 |
| 13.3 | Protocol Deviations | 53 |
| 13.4 | Publication and Data Sharing Policy | 54 |
| 14 | PROTOCOL AMENDMENT HISTORY..... | 54 |
| 15 | LITERATURE REFERENCES | 59 |

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

ABBREVIATIONS

| | |
|---------|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CAO | Chronic Airflow Obstruction |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data and Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| ECOPD | Exacerbation of Chronic Obstructive Pulmonary Disease |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FEV1 | Forced Expiratory Volume in 1 second |
| FFR | Federal Financial Report |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practice |
| GWAS | Genome-Wide Association Studies |
| HIPAA | Health Insurance Portability and Accountability Act |

| | |
|---------|---|
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |
| LSMEANS | Least-squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PBRN | Practice-Based Research Network |
| PI | Principal Investigator |
| PRISm | Preserved ratio, impaired spirometry |
| QA | Quality Assurance |
| QC | Quality Control |
| RE-AIM | Reach, Effectiveness, Adoption, Implementation, Maintenance |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SNO | Symptomatic non-obstructed |
| SOA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |
| USPSTF | United States Preventive Services Task Force |

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

| | |
|---------------------------|--|
| Title: | The CAPTURE Study: Validating a unique Chronic Obstructive Pulmonary Disease (COPD) case finding tool in primary care |
| Study Description: | <p>Aims 1 and 3. A prospective, multicenter study including a cross-sectional validation to define sensitivity and specificity of CAPTURE and its impact on clinical care across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and peak expiratory flow (PEF) measurement, designed to identify undiagnosed patients with Chronic Obstructive Pulmonary Disease (COPD).</p> <p>Aim 2. This study delivers a qualitative assessment of clinical practice acceptance of and implementation strategy for CAPTURE case finding within 10 varied primary care practices across 5 US PBRN regions. We evaluate primary care practice attitudes, beliefs and recommendations about CAPTURE's potential to feasibly integrate into clinical practice patterns, workflow and quality improvement paradigm planning in a variety of primary care clinical settings.</p> |
| Definitions: | <p>CAPTURE+ = Participants with</p> <ul style="list-style-type: none">• CAPTURE score ≥ 5, or• CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females <p>CAPTURE- = Participants with CAPTURE score < 2 or scores 2-4 with normal PEF, defined as ≥ 350 L/min for males and ≥ 250 L/min for females</p> <p>Spirometrically defined COPD = Participants with abnormal spirometry, defined as post-bronchodilator $FEV_1/FVC < 0.7$. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV_1/FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study.</p> <p>Clinically significant COPD = Participants with abnormal spirometry, defined as post-bronchodilator $FEV_1/FVC < 0.7$, plus one of the following:</p> <ul style="list-style-type: none">• $FEV_1 < 60\%$ predicted, or• ≥ 1 exacerbation-like event within the past 12 months. <p>Mild COPD = Participants with abnormal spirometry, defined as post-bronchodilator $FEV_1/FVC < 0.7$ plus both of the following:</p> <ul style="list-style-type: none">• $FEV_1 \geq 60\%$ and• No prior history of ECOPD <p>Preserved ratio, impaired spirometry (PRISm) = Participants without spirometrically defined COPD who have post-bronchodilator $FEV_1 < 80\%$ predicted.</p> <p>Symptomatic non-obstructed (SNO) = Participants without spirometrically defined COPD and without PRISm who have a COPD Assessment Test score ≥ 10.</p> |

| | |
|--------------------|--|
| Objectives: | Aims 1 and 3 Primary Objectives: <ul style="list-style-type: none">• Aim 1 - Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. |
| | <ul style="list-style-type: none">• Aim 3 – Define the impact of CAPTURE information provided to clinicians in identifying and managing CAPTURE+ patients across a broad range of primary care settings. <p>Aim 2 Primary Objective: Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.</p> |

| | |
|--|--|
| | <p>Aims 1 and 3 Secondary Objectives:</p> <ul style="list-style-type: none">• Aim 1 –• Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic groups in a range of primary care settings.• Determine positive and negative predictive values (PPV and NPV) in different practice settings.• Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with PEF measurements for identifying undiagnosed COPD.• Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD.• Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD including:<ol style="list-style-type: none">1) spirometry-defined COPD, and2) mild COPD• Determine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach. <p>• Aim 3 -</p> <ul style="list-style-type: none">• Define the impact of providing CAPTURE education and patient-level CAPTURE information to clinicians on selected clinician interventions for the management of CAPTURE+ patients.• Assess the impact of CAPTURE education and patient-level CAPTURE information on clinician interventions specific to smokers who are CAPTURE+.• Determine the impact of CAPTURE education and patient-level CAPTURE information on patient symptoms, exacerbations, hospitalizations, and mortality among CAPTURE+ patients.• Determine the impact of CAPTURE education and receipt of patient-level CAPTURE information on identification and management of patients with respiratory burden.• Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening. <p>Aim 2 Secondary Objectives:</p> <ul style="list-style-type: none">• Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. |
|--|--|

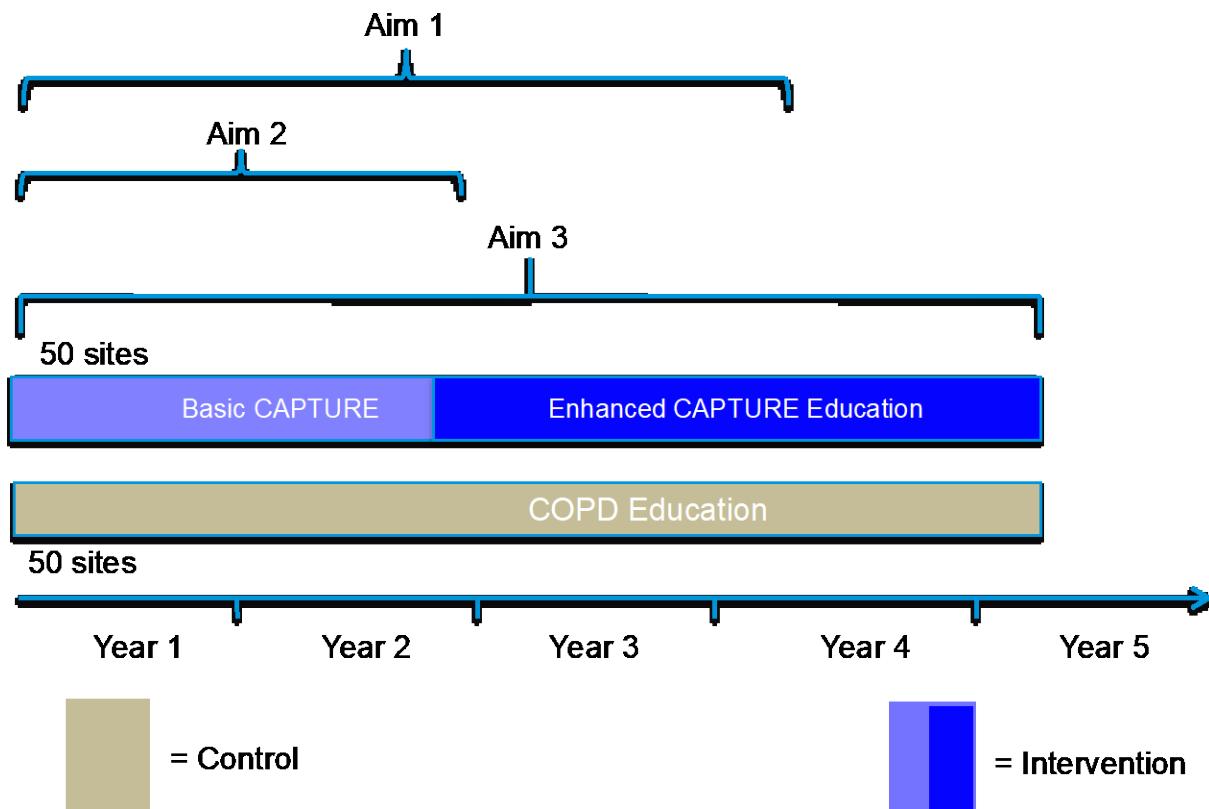
| | |
|-------------------|--|
| | <ul style="list-style-type: none">Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics.Determine the potential impact of SARS CoV-2 infection on the application of the CAPTURE approach. |
| Endpoints: | <p>Aims 1 and 3 Primary Endpoints:</p> <ul style="list-style-type: none">Aim 1 –<ul style="list-style-type: none">Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline.Aim 3 –<ul style="list-style-type: none">Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/treatment, or 5) referral for or completion of pulmonary rehabilitation. <p>Aim 2 Primary Endpoints:</p> <ul style="list-style-type: none">Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice.Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians.Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types. <p>Aims 1 and 3 Secondary Endpoints:</p> <ul style="list-style-type: none">Aim 1 –<ul style="list-style-type: none">Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational level.Positive and negative predictive values (PPV and NPV) in different practice settings.Areas under the receiving operator characteristic curve (AUC) for various cutpoints of CAPTURE and PEF₁ measurements to determine the best cutpoint for COPD+ screen.AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD.All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPDAim 3 –<ul style="list-style-type: none">Proportion of CAPTURE+ participants who have each of the following occur within 12 months of study baseline (separate endpoints to be evaluated individually): 1-5) each component of the Aim 3 primary endpoint, and 6) recommendation or administration of influenza vaccination. |

| | |
|--------------------------|---|
| | <ul style="list-style-type: none">○ Proportion of CAPTURE+ participants currently smoking at the baseline study visit who have any of the components of the Aim 3 primary endpoint or any of the following occur within 12 months of baseline (evaluated as a composite endpoint and as individual endpoints): 1) clinician counseling or recommendation for smoking cessation, 2) referral to a smoking cessation program, 3) referral to a smoking quit line, and 4) newly prescribed medication for smoking cessation.○ In CAPTURE+ participants, change in CAT score between baseline and follow-up at 12 months after baseline, and proportion of patients who experience exacerbations, hospitalizations, or mortality within 12 months of baseline.○ All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) Mild COPD, 4) preserved ratio, impaired spirometry (PRISM), and 5) symptomatic non-obstructed (SNO).○ All of the above endpoints for Aim 3, in all of the analysis populations named above, separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic. <p>Aim 2 Secondary Endpoints:</p> <ul style="list-style-type: none">● Existing COPD screening and diagnostic and case finding processes within a variety of primary care practices.● Primary care practice belief about capacity to change from existing COPD screening and diagnostic assessment strategies.● Practice-specific COPD screening and diagnostic continuing education preference. |
| Study Population: | <p>Aims 1 and 3. Adults 45-80 years old without a prior diagnosis of COPD (total N ~ 5000)</p> <p>Aim 2.</p> <ul style="list-style-type: none">- 10 primary care practices: 2 practices per PBRN with up to 15 clinical staff participants per practice; clinician N = up to 150 (up to 30 clinician participants per PBRN).- Aim 1 patient opinion survey population; patient N = 200 (40 patients from each PBRN; adults 45-80 years old, without a prior diagnosis of COPD).- Total N = up to 350 |
| Phase: | N/A |

| | |
|--|--|
| Description of Sites/Facilities Enrolling Participants: | <p>Aims 1 and 3. Enrollment will occur in approximately 100 primary care practices affiliated with 7 primary care based practice networks (PBRN) across the United States who exhibit a broad range of gender, ethnic, racial, socioeconomic, and regional diversity.</p> <p>Aim 2.</p> <ul style="list-style-type: none">• Two primary care practices chosen by each of the same 5 PBRN co-investigator teams make up the 10 aim 2 practices from which clinician participants are enrolled. These 10 practices are separate from the 100 chosen practices in aims 1 and 3.• Patient participants are a sub-sample of those participants enrolled in aims 1 and 3. |
| Description of Study Intervention: | <p>Aims 1 and 3. Primary care practices will be randomized to either receive basic COPD education and patient-level CAPTURE information with CAPTURE education (initially basic then later enhanced based on data collected in Aim 2) versus COPD education only.</p> <p>Aim 2. Participating primary care clinicians from 10 varied practices are surveyed at three different time points and participate in two focus groups qualitatively assessing CAPTURE implementation strategy and COPD case finding approaches in primary care. Participating patients complete one 10-minute written opinion survey about CAPTURE.</p> |
| Study Duration: | <p>Aim 1 and 3. 4 years</p> <p>Aim 2. 2 years</p> |
| Participant Duration: | <p>Aims 1 and 3. Up to 12 months</p> <p>Aim 2.</p> <ul style="list-style-type: none">• Primary care practice clinicians: questionnaires and focus groups (total 3 hours/participant) over 16 months.• Primary care patients: one 10-minute questionnaire/participant over 14 months. |

1.2 SCHEMA

FIGURE 1. OVERALL STRUCTURE OF AIMS



CAPTURE COPD Study Time Commitment

CAPTURE COPD: The Primary Care Practice Expert Panel Study will take place in 10 practices in 5 regions in the US. Central to the success of CAPTURE COPD is the role of clinical staff expertise in providing feedback, information and suggestions about clinical workflow for COPD diagnosis.

| | | |
|---|--|-------------|
| Introductory Phone Call | Brief phone call with CAPTURE research team to review the CAPTURE COPD: The Primary Care Practice Expert Panel aim. Discussion includes: review of the research content, timeline and scheduling of the half-day site visit for February/March 2018 | Month 1 |
| In Person Baseline Assessment/ Site Visit: | SITE VISIT INCLUDES: <ul style="list-style-type: none">Walk through of practice and staff introduction: 2 clinical staff with CAPTURE team [60 minutes]Clinic flow observation and mapping [1/2 day]Post clinic flow observation Q&A: 2 clinical staff and CAPTURE research team [30 minutes]CAPTURE COPD information distribution and consent process | Month 2-3 |
| Online Questionnaire: 1st of three | Online/written questionnaire at baseline [20 minutes] | |
| State-of-the-Art COPD Web-based Continuing Education | Three modules encouraged; All modules optional 20 minutes/module; per Aim 3 description | Month 3-7 |
| Practice Expert Panel Focus Group #1 | Prescribers and Non-Prescribers (2 different days) 60 minute focus group | Month 6-10 |
| Online Questionnaire: 2nd of three | Online/written questionnaire at 6 months [20 minutes] | |
| Online Questionnaire: 3rd of three | Online/written questionnaire at 12 months [20 minutes] | Month 11-14 |
| Practice Expert Panel Focus Group #2 | Pooled prescribers and Non-Prescriber Clinical Staff [60 minutes] | Month 14-16 |



Randall W. Brown, M.D., MPH, AE-C
UM, School of Public Health
1415 Washington Heights, Room 2824
Ann Arbor, MI 48109 - 2029
Email: rbrownmd@umich.edu

Lara J. Thomas, MPH
UM, School of Public Health
1415 Washington Heights, Room 2811
Ann Arbor, MI 48109 - 2029
Email: ljthomas@umich.edu

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities (Aims 1 and 3)

| | Pre-Visit Contact ¹ | Baseline | 12 Months ³ |
|--|---|-------------------------------------|------------------------|
| Contact (C)/ Visit (V)/Medical Record Review (MRR) | C1 | V1 | C2/MRR ⁵ |
| Time point, days (Visit window) | Prior to outpatient visit (≤ -1) | Within 30 days of pre-visit contact | 365 \pm 30 (C2) |
| Contact patient re: interest in study visit ¹ | X | | |
| Informed consent | | X | |
| Demographics | | X | |
| Medical history (Co-morbidities) ² | | X | |
| Vaccination status | | X | X |
| CAPTURE 5-item questionnaire | | X | X |
| CAPTURE item additional questionnaire | | X | X |
| Peak Expiratory Flow (PEF) | | X | |
| Height and weight | | X | |
| Respiratory medications review | | X | X |
| Spirometry ⁴ | | X* | |
| Respiratory symptoms, exacerbation assessment | | X | X |
| Smoking exposure history | | X | |
| Smoking cessation review ⁶ | | | X |
| COPD Assessment Test (CAT) | | X | X |
| COVID-19 Questionnaire | | X | X |
| Adverse Events | | X | |
| Medical record review Additional COVID-19 items | | | X X |

1. Optional per site recruitment preferences
2. Comorbidities including cardiovascular, respiratory and malignant disorders
3. Recorded for a subset of participants who meet any of the following criteria: 1) CAPTURE+ subjects defined as CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as post-bronchodilator FEV₁/FVC < 0.70 or FEV₁ $< 80\%$ predicted at baseline, or pre-bronchodilator FEV₁/FVC < 0.65 or FEV₁ $< 70\%$ predicted for patients who do not complete post-bronchodilator spirometry; and, 3) a random sample of approximately 5% of those who do not meet criteria 1 and 2. For participants meeting criteria 1 and 2 who cannot or choose not to complete the 12-month assessment, medical record review will still be completed. For participants meeting criteria 1 and 2 who

change medical practices and medical record review cannot be completed, patients will be contacted for completion of patient reported data.

4. Pre-bronchodilator spirometry will be done for all participants. Post- bronchodilator spirometry will be performed for participants with abnormal spirometry ($FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted) *If the participant has taken a bronchodilator within a 2-hour window of spirometry the spirometry will be considered post-bronchodilator and a pre-bronchodilator spirometry will not be done.

5. The 12-month assessment consists of patient reported data, collected by the COPD Foundation, and medical record review completed by site coordinators.

6. This will be completed in those that are smoking at V1.

2 INTRODUCTION

2.1 STUDY RATIONALE

Undiagnosed COPD is a leading cause of morbidity and mortality. Spirometry, the 'gold standard' for diagnosis, is not recommended for screening in asymptomatic individuals or untargeted case finding and remains widely underutilized in primary care settings. Targeted case finding approaches have been strongly advocated but currently available approaches generally identify patients across the spectrum of mild to severe disease without reference to potential therapeutic benefit or exacerbation risk, thereby limiting clinical impact and acceptance in primary care. There is an urgent need to develop and implement simple case finding approaches that can identify patients with clinically significant COPD in primary care settings.

Through a multi-stage, iterative process we developed a simple case finding tool using five questions combined with selective peak expiratory flow (**PEF**) measurement that identifies individuals with 1) an $FEV_1 < 60\%$ predicted and/or 2) at risk for ECOPD. We call this tool CAPTURE (**COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk**)(1). As clinical trials have demonstrated benefit and therapeutic guidelines recommend therapy for these individuals we have labeled these patients as suffering from 'clinically significant' COPD. The long-term goal of this project is to identify these patients so that they can be treated and result in improved health status, reduced exacerbations, and decreased morbidity.

The overall objectives of Aims 1 and 3 of this project are to 1) validate the sensitivity, specificity, and predictive value of CAPTURE to identify undiagnosed, clinically significant COPD patients in a diverse primary care population; and explore whether identifying these patients results in improved COPD specific care and health status. Our principal hypothesis is that CAPTURE can effectively and efficiently identify primary care patients with undiagnosed, clinically significant COPD. We objectively test our principal hypothesis by completing to two separate and linked aims:

Aim 1 – Determine the sensitivity and specificity of CAPTURE in identifying clinically significant COPD patients in a broad range of primary care outpatient practices.

Working hypothesis - A simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.

We will conduct a cohort study of approximately 5,000 participants in 100 primary care practices affiliated with five primary care based research networks (**PBRN**) that provide access to previously undiagnosed patients with clinically significant COPD who exhibit gender, ethnic, racial, socioeconomic and regional diversity.

Aim 3 – Define the impact of CAPTURE screening in a broad range of primary care outpatient practices and evaluate practice and patient characteristics that are associated with care implementation and clinical outcomes for patients with respiratory symptoms (CAPTURE+).

Working hypothesis – Provision of patient specific CAPTURE data to practicing clinicians will result in improved management of patients with respiratory symptoms (CAPTURE+).

We will provide basic COPD education and patient level CAPTURE information and education to site clinicians at 50 of the sites and prospectively follow selective, pre-defined subgroups of patients to define relevant outcomes. Care at the other 50 clinical sites will follow standard of care with basic COPD education to clinicians.

Assessing the potential clinical impact of a novel COPD case finding strategy includes confirmation of validity in a diverse primary care patient population and a quantitative research evaluation of its impact on clinical decision-making and COPD patient outcomes, as found in aims 1 and 3 above. Equally important is exploration through validated implementation methods that the newly designed CAPTURE tool, even if valid and impactful, can provide real-world utility within a variety of primary care practice settings. While we find no evidence in previous COPD screening studies of such detailed appraisal, ascertaining the feasibility of clinical testing is a vital component of assuring that new approaches address potential clinical practice need, capacity, knowledge and diagnostic gaps. As much as possible, clinical respiratory innovations should align with busy workflow at all practice staff levels to more effectively identify primary care patients with undiagnosed, clinically significant COPD. The SARS-CoV-2 pandemic may potentially alter the approach to COPD Case Finding in the primary care community; the protocol has been adapted to investigate this possibility. Similarly, the potential of SARS-CoV-2 infection and the COVID-19 clinical syndrome to impact respiratory symptoms in primary care patients will also be explored.

To maximize success of the CAPTURE adoption, education and implementation in this study and in future work, Aim 2 is introduced to assess practice experience, need and preference that can inform clinical COPD case finding and education in primary care settings:

Aim 2 – Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices.

The *overall objective* of this aim is to qualitatively explore primary care clinical practice acceptance of COPD case finding implementation and define education and feasibility strategies to enhance adoption in primary care practice. This assessment includes understanding clinician and clinical staff COPD practice and perceptions in addition to the feasibility of case finding integration into existent clinical work patterns. To attain this objective, we address one *working hypothesis* – a COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms in a variety of primary care clinical settings. The *rationale* for this objective reflects the importance of establishing if an innovative approach to COPD case finding (CAPTURE) is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings.

With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding with informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

2.2 BACKGROUND

Aims 1 and 3.

COPD remains a major cause of morbidity and mortality. COPD results in substantial morbidity and mortality worldwide.(2-4) Globally, the prevalence of COPD and years lived with disability increased from 1990 to 2013.(5) This is particularly evident in older individuals.(6) These well-designed population based studies confirm the growing impact of COPD.

COPD is frequently undiagnosed. We recently documented that only 28% of participants with chronic airway obstruction (**CAO**) had physician diagnosed disease.(7) Importantly, an $FEV_1 < 50\%$ predicted was noted in 10% of those with undiagnosed CAO; this is similar to other cohorts or population based surveys.(8-11) There is consistency in these well-conducted studies that confirm most COPD patients are undiagnosed.

Spirometry is underutilized. The U.S. Preventive Services Task Force (**USPSTF**) recently recommended against the use of spirometry for routine, general population or practice-based screening in asymptomatic individuals.(12) An editorial by the PI of this application highlighted the limitations of this conclusion.(13) Within primary care spirometry is often viewed as time consuming and difficult to implement and interpret.(14) As such, it is not routinely used.(15-19) Even the availability of less expensive and easily used spiroometers(20) has not resulted in increased utilization.(21, 22)

Undiagnosed COPD is associated with a negative clinical impact. In a robust, population based study we confirmed that undiagnosed patients experienced impaired health status and a higher risk for all-cause mortality compared to those without CAO; this was particularly evident with more severe CAO.(7) Others have confirmed increased mortality,(23) health status impairment,(24) exacerbation-like respiratory events,(11) and increased health care costs.(25, 26) As such, there are consistent data suggesting that undiagnosed COPD patients experience negative clinical events and impaired health status.

Therapeutic interventions improve COPD clinical outcomes. Well designed, randomized controlled trials confirm that COPD therapy is effective, particularly in patients with an $FEV_1 < 60\%$ predicted who are symptomatic or at risk for ECOPD.(27, 28) Despite limited data, some have suggested that earlier detection of patients with previously undiagnosed, yet clinically significant COPD, in primary care settings could improve short- and long-term patient outcomes and may be cost-effective. (29, 30)

COPD case finding approaches to date have generally been methodologically limited. Several COPD case finding tools have been created based on existing epidemiologic literature or expert opinion.(31, 32) This includes tools created by investigators in this study.(33, 34) In general, current approaches were designed to identify COPD patients without reference to disease severity or ECOPD risk, resulting in the identification of a high proportion of patients with mild or minimally symptomatic disease.(21, 33-39) Several studies have tested the accuracy of handheld flow meters for case identification with varying sensitivity and specificity.(40) Although informative in terms of CAO, PEF meters have been unable to systematically identify patients at risk of ECOPD. We tested a three-staged approach (risk-factor

questionnaire, PEF, and spirometry) for identifying moderate to severe COPD ($FEV_1 < 60\%$ predicted) in a convenience sample of the general population.(41) This study was limited by the nature of the population screened and the screening questionnaire used but supported the concept that PEF can facilitate COPD case finding.

A systematic analysis of existing databases provides insight into the best variables for COPD Case Identification. To identify potential items that could be useful in the identification of undiagnosed COPD we interrogated three robust datasets of populations in which the investigators on this application had major roles [COPD Foundation Peak Flow Study Cohort (n=5761); Burden of Obstructive Lung Disease Kentucky site (n=508); and COPDGene® (n=10,214)].(42) We utilized the machine learning statistical method of random forests to identify and validate variables most important in identifying patients with clinically significant COPD. COPD case finding candidate content included items reflecting exposure, personal and family history, respiratory symptoms, recent health history, activity limitation and demographics.

A comprehensive, qualitative study identified key constructs for identifying recently diagnosed patients with clinically significant COPD. We completed a two phase study that included focus groups followed by cognitive interviews to refine the key constructs for identifying patients with clinically significant COPD.(43) Fifty participants were recruited including those with mild airflow obstruction, diagnosed within the previous six months and without previous ECOPD; those diagnosed within the previous six months and with a history of at least one ECOPD within the prior year; those with 2-3 risk factors for COPD but without CAO; and those with ≥ 4 risk factors for COPD but without CAO. Using a content analysis approach, key themes and constructs were identified and integrated with the content of the previous literature review and data mining. We identified 44 candidate items that resonated with patients and provided important insights into a case finding instrument.

A five-item questionnaire exhibits excellent operating characteristics to identify clinically significant COPD patients. We completed a prospective, multi-site, case-control study of four groups: cases with clinically significant COPD – COPD with ≥ 1 ECOPD in the previous year (n=97) and COPD with no ECOPD but an $FEV_1 < 60\%$ predicted (n=89); controls – no known COPD (n=87) and COPD with an $FEV_1 > 60\%$ predicted and no ECOPD in the previous year (n=74). Using random forest analyses the 44 candidate items were reduced to 34-item, 21-item, 8-item and two different five-item sets. Through-out the item reduction process, the item sets maintained good performance, consistently misclassifying fewer than 27% of cases and controls, and with sensitivity greater than 80% and specificity greater than 70%. A five-item questionnaire exhibited good operating characteristics for separating COPD cases from controls. These characteristics were even better when separating COPD from controls without COPD.

Selective PEF measurement enhances the operating characteristics of a COPD case finding strategy. In the above case control study PEF was measured using a mechanical PEF meter with disposable mouthpieces. To optimize sensitivity and specificity, the following cut-off scores were selected, based on our data, for identifying cases of clinically significant COPD using PEF alone: males: < 350 L/min; females: < 250 L/min. The best method for predicting cases was a combination of the questionnaire and PEF (**CAPTURE**), where PEF is used only for mid-range scores. Under this scoring scenario, patients with scores of 0 or 1 are not considered at risk of clinically significant COPD; they would not require further evaluation. Those with a score of 5 or 6 are considered to be at high risk of clinically significant COPD and should be referred directly for further evaluation, including clinical spirometry. Patients scoring in the middle range (2 to 4) would undergo PEF testing, applying the 350/250 interpretation thresholds. In our sample, 52% of the participants required PEF to determine if spirometry was indicated. The other 48% needed only the five-item questionnaire. This approach provided 90% sensitivity, 93% specificity and an overall error rate of 9%.

CAPTURE exhibits similar operating characteristics in a Spanish speaking population. To broaden our target population, the five-item questionnaire was methodically translated to Spanish using previously validated, rigorous methods(44) to yield an instrument that is equivalent to the English questionnaire and linguistically and culturally applicable to persons of diverse Spanish-speaking backgrounds residing in the US. In a subset of Spanish speaking participants CAPTURE exhibited excellent sensitivity (88%), specificity (92%) and overall error rate (10%) for identifying patients with clinically significant COPD.

Aim 2.

Consistent with national criteria for preventive and chronic disease care quality, feasibility science is designed to assist clinical and health education evaluators plan for assessing and evaluating specific implementation factors essential to the success of new diagnostic, therapeutic and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics in chronic disease diagnosis and management. The aim addresses through the RE-AIM feasibility approach how a new tool might a) identify target populations (Reach); b) appraise optimal targeted respiratory history and symptoms consistent with clinically significant COPD (Effectiveness or Impact); c) integrate into practice workflow (Adoption); d) deliver changes and improvements to COPD care within the scope of real-world clinical practice (Implementation); and e) persist in use and quality over time (Maintenance) (45-53).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks associated with Aims 1 and 3 of this study are outlined below.

Spirometry: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Albuterol: Tremulousness, feeling of a strong, rapid heartbeat, and palpitations can occur with inhaled albuterol. A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication. Note that albuterol is only administered to those with abnormal spirometry on the baseline spirometry assessment (defined as $FEV_1/FVC < 0.70$ or $FEV_1 < 80\%$ predicted).

Peak Expiratory Flow: Participants may become short of breath. Syncope, light-headedness and fainting may develop during this test. These are uncommon.

Other non-physical risks of the study include those from economic loss from participation in the study; this will be minimized by scheduling tests and evaluations in a timely manner in the fewest number of visits possible. Patient and physician participants will be provided a modest fee to cover their time to participate in the study.

We anticipate few adverse events due to the non-invasive nature of the study procedures and the rarity of such events encountered during the initial visits and longitudinal follow-up. Medical care will be available at each Clinical Center to treat participants who develop adverse events during in-person study visits.

Potential risks associated with Aim 2 of this study include:

No more than minimal risk exists for participants within aim 2.

Confidentiality of information and identification are the risks associated with this project. Based on previous research and the protocols that have been developed, we believe that the likelihood of these risks to the participants would be minimal, i.e. "rare".

Potential risks associated with the study (all Aims) include:

Loss of confidentiality of study data: This is unlikely since data collected will be stored in locked file cabinets in locked rooms at the Clinical Centers. In addition, only participant IDs are used to identify participants in the secure server at the Data Coordinating Center.

Poor quality data: If the data collected are of poor quality such that it is not useable to achieve study aims, participants will have unnecessarily been exposed to other risks in the study.

2.3.2 KNOWN POTENTIAL BENEFITS

For Aims 1 and 3 of this study, participants could receive direct benefit as a result of their participation in this research. Current state-of-the-art COPD education is offered to all clinicians at participating PBRN sites (see aim 3 protocol) that could result in improved care for their COPD patients. Health care providers at practices randomized to the CAPTURE education arm (arm 1), will receive their participant's CAPTURE Tool scores and peak flow results. This may result in further diagnostic testing leading to a diagnosis of COPD or other respiratory disorder.

Known potential benefits for each participating clinical staff include critical review their clinical respiratory practice. In general, aim 2 offers the ability to assess and address CAPTURE-specific primary care practice feasibility issues which could augment or hamper clinical communication or implementation of COPD case-finding in real-world primary care clinical practice.

Potential benefits to society include improved understanding of how best to identify individuals with COPD in the primary care setting. This could ultimately lead to better treatments and lower morbidity and mortality for patients with COPD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The demonstrated and potential future benefits to improved understanding of COPD case finding outweigh the minimal risks of the procedures performed.

Increased understanding of how best to diagnose individuals at risk for COPD in the primary care population has the potential to benefit both patients with COPD and society at large. The risk to individuals associated with this study protocol is small and the knowledge to be gained is substantial.

3 OBJECTIVES AND ENDPOINTS

Aims 1 and 3.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|--|---|--|
| Primary | | |
| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
| Aim 1: Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with <i>clinically significant COPD</i> in a broad range of primary care settings | Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with clinically significant COPD at baseline. | Standard methodology for COPD diagnosis will be used (1). |
| Aim 3: Define the impact of CAPTURE information provided to clinicians in identifying and managing CAPTURE+ patients across a broad range of primary care settings. | Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/treatment, or 5) referral for or completion of pulmonary rehabilitation. | The composite endpoint is clinically relevant and consistent with published data (45). This will test the impact of CAPTURE on clinician behavior. |
| Secondary | | |
| Aim 1: Define the sensitivity and specificity of CAPTURE for patients with COPD across a broad range of racial and ethnic subgroups in a range of primary care settings | Sensitivity and specificity of CAPTURE to identify previously undiagnosed patients with COPD across sex, ethnic groups, urban vs rural location, and educational status. | Patient characteristics will be used to assess the robustness of CAPTURE. |
| Aim 1: Determine positive and negative predictive values (PPV and NPV) in different practice settings. | Positive and negative predictive values (PPV and NPV) in different practice settings. | PPV and NPV will be used to assess the robustness and usefulness of CAPTURE in various settings. |

| | | |
|--|--|---|
| Aim 1: Verify the optimal use (cutoff threshold) of the CAPTURE tool in combination with FEV ₁ measurements for identifying undiagnosed COPD. | AUC for various cutpoints of CAPTURE and PEF measurements to determine the best cutpoint for clinically significant COPD screen. | The best discrimination for CAPTURE combined with FEV ₁ will indicate the optimal usage of the tool. |
|--|--|---|

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|--|---|---|
| Aim 1: Determine patient and site characteristics that, with the CAPTURE assessment, will best identify persons with undiagnosed COPD. | AUC to identify the combination of patient/site characteristics which best discriminates those with clinically significant COPD. | The best discrimination will determine which site and patient characteristics best predicted undiagnosed COPD in combination with the CAPTURE tool. |
| Aim 1: Determine whether CAPTURE is useful in identifying other definitions of undiagnosed COPD: 1) spirometry-defined COPD, and 2) mild COPD | All primary and secondary endpoints as applied to 1) spirometry-defined COPD and 2) mild COPD | This will determine the robustness of the CAPTURE tool. |
| Aim 3: Define the impact of providing CAPTURE education and patient-level CAPTURE information to clinicians on selected clinician interventions for the management of CAPTURE+ patients. | Proportion of CAPTURE+ participants who have each of the following occur within 12 months of study baseline (separate endpoints to be evaluated individually): 1-5) each component of the Aim 3 primary endpoint, and 6) recommendation or administration of influenza vaccination. | Each endpoint is clinically relevant and consistent with published data. (45) This will test the impact of CAPTURE on clinician behavior. |
| Aim 3: Assess the impact of CAPTURE education and patient-level CAPTURE information on clinician interventions specific to smokers who are CAPTURE+. | Proportion of CAPTURE+ participants currently smoking at the baseline study visit who have any of the components of the Aim 3 primary endpoint or any of the following occur within 12 months of baseline (evaluated as a composite endpoint and as individual endpoints): 1) clinician counseling or recommendation for smoking cessation, 2) referral to a smoking cessation program, 3) referral to a smoking quit line, and 4) newly prescribed medication for smoking cessation. | Certain outcomes are specific to only smokers and should be assessed. |
| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
| Aim 3: Determine the impact of CAPTURE education and patient-level CAPTURE information on patient symptoms, exacerbations, hospitalizations, and mortality among CAPTURE+ patients. | In CAPTURE+ participants, change in CAT score between baseline and follow-up at 12 months after baseline, and proportion of patients who experience exacerbations, hospitalizations, or mortality within | These endpoints are important for quality of life and long-term patient outlook. |

| | | |
|--|---|---|
| | 12 months of baseline. | |
| Aim 3: Determine the impact of CAPTURE education and patient-level CAPTURE information on identification and management of patients with respiratory burden. | All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) Mild COPD, 4) preserved ratio, impaired spirometry (PRISm), and 5) symptomatic non-obstructed (SNO). | This will assess the overall effect of CAPTURE screening in clinically relevant populations. |
| Aim 3: Determine the potential impact of SARS CoV-2 infection on clinical actions taken in response to CAPTURE screening. | All of the above endpoints for Aim 3, in all of the analysis populations named above, separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic. | Clinician behaviors likely were affected by the presence of a pandemic involving respiratory illness. |

Aim 2.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| Primary | | |
| Explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. | <p>Primary care clinician recommendations that inform CAPTURE RE-AIM strategies at both provider and clinical support levels of primary care practice.</p> <p>Primary clinician recommendations that inform CAPTURE-associated COPD education models for primary care clinicians.</p> <p>Primary care clinician recommendations that inform CAPTURE-associated COPD clinical quality improvement designs across a variety of primary care practice types.</p> | Clinical improvement models that introduce new testing must investigate practice opinion and behavior and incorporate clinician recommendation. |

| Secondary | | |
|--|--|--|
| Qualitatively assess primary care clinical staff COPD practice behavior – including COPD screening and diagnostic perceptions, beliefs and knowledge – that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. | Existing COPD screening and diagnostic and case-finding processes within a variety of primary care practices. Primary care practice beliefs about capacity to change from existing COPD screening and diagnostic assessment strategies. Practice-specific COPD screening and diagnostic continuing education preference. | Awareness of existing clinician knowledge and behavior can influence workflow implementation and overall effectiveness of new clinical tools. |
| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
| Qualitatively assess primary care patient opinion of CAPTURE COPD case finding that will inform strategies to improve CAPTURE RE-AIM (reach, impact, adoption, implementation and maintenance of use) characteristics. | CAPTURE opinion survey ascertaining participant comprehension of CAPTURE instructions and testing and ease of completion. | Patient satisfaction, understanding and ease of test completion affects staff implementation and workflow decision. Participant opinion survey results will seed CAPTURE implementation planning practice staff focus groups. |

4 STUDY DESIGN

4.1 OVERALL DESIGN

A prospective, multicenter study that includes three key aims: 1) cross-sectional validation to define sensitivity and specificity of CAPTURE; 2) *qualitative* research exploration engaging clinical staff at all levels from primary care practices serving US patient populations of differing gender, racial, ethnic, urban/rural and socio-economic blends, and 3) explore the impact of CAPTURE on clinical care and patient outcomes across a broad range of primary care settings in a cluster randomized controlled clinical trial. The CAPTURE tool consists of a 5-item self-administered questionnaire and selected use of peak expiratory flow (PEF) measurement, designed to identify clinically significant Chronic Obstructive Pulmonary Disease (COPD).

For Aim 1, approximately 5,000 patients will be recruited at the time of their regularly-scheduled appointment across 100 participating primary care clinics associated with practice-based research networks (PBRNs). Eligible participants will undergo a baseline visit during which the CAPTURE tool and spirometry will be obtained, as well as PEF and other participant characteristics.

For Aim 2, approximately 150 clinicians from 10 participating primary care practices across 5 US PBRNs will undergo detailed implementation investigation of the CAPTURE case finding model for clinically significant COPD. In addition, 200 primary care patients recruited as part of Aim 1 will complete a 10- NIH-FDA Clinical Trial Protocol Template – v1.0 7 Apr 2017

minute written CAPTURE opinion survey.

To address Aim 3, participating primary care practices will be randomized in a 1:1 fashion to one of the following interventions:

- Arm 1: Practice clinicians will receive basic COPD education, and patient-level CAPTURE information with CAPTURE interpretation education (CAPTURE+ COPD education). As the second aim addresses the optimal format for delivering practice CAPTURE education this will be incorporated at the sites randomized to this arm (see Enhanced CAPTURE education in Figure 1).
- Arm 2: Practice clinicians will receive basic COPD education only (COPD education).

Basic COPD and CAPTURE specific education will use an interactive, web-based education program which will be provided to all practice personnel, including physicians, nurse practitioners, physician assistants, nurses, medical assistants, clerical staff and administrative staff. Practitioners at sites randomized to the CAPTURE+COPD education intervention will receive the CAPTURE score from the central study coordinators soon after the baseline assessments have been completed.

Addressing Aims 1 and 3 will include a baseline visit for all participants and for Aim 3 longitudinal follow-up over 12 months for a predefined cohort of participants. Determination of the participants included in the longitudinal follow-up cohorts will be made after the baseline visit.

Baseline Data

Practices and/or study staff will pre-screen patients according to local guidelines to identify potential participants based on the following criteria: no prior COPD diagnoses, between 45 and 80 years old, and speak and read either English or Spanish. The timing of the pre-screening and the method to approach these patients for participation in the study (e.g., at the next outpatient visit, via telephone) will be flexible, depending upon site recruitment preferences. Patients who are eligible based on the pre-screening questions and agree to participate in the study will sign informed consent. After signing the consent, they will complete the CAPTURE questionnaire, PEF testing, spirometry testing, other respiratory questionnaires, and provide past medical history and demographic information. Local/PBRN study coordinators for each of the 7 PBRNs will perform the study procedures and record baseline information into the electronic data capture (EDC) system.

The EDC system will calculate a CAPTURE score for each participant, based on his/her CAPTURE questionnaire answers and PEF measurement. A binary score (positive or negative CAPTURE) will be emailed to the central study coordinator only for participants randomized to CAPTURE+COPD education intervention practices. The coordinator will communicate this information to these practitioners. Practitioners at sites randomized to the COPD education only intervention will be blinded to CAPTURE scores. Practitioners in both intervention arms will be blinded to research spirometry results.

Analyses will include a comparison of CAPTURE scores with data from spirometry testing and participant reported data to determine sensitivity and specificity of the CAPTURE tool. *The hypothesis is that a simple case finding methodology using a five-item questionnaire with selective PEF measurement will identify undiagnosed patients with clinically significant COPD.*

Based on the data collected at baseline, participants will be classified into the following groups for analyses:

| Cohort | Definition |
|--|---|
| CAPTURE+ | Participants with <ul style="list-style-type: none"> CAPTURE score ≥ 5, or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females |
| CAPTURE- | Participants with <ul style="list-style-type: none"> CAPTURE score < 2 or scores 2-4 with normal PEF (defined as ≥ 350 L/min for males and ≥ 250 L/min for females) |
| Spirometrically defined COPD | Participants with abnormal spirometry, defined as post-bronchodilator FEV ₁ /FVC <0.7 . If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV ₁ /FVC is less than 0.65, the participant will be considered to have COPD for the purpose of follow-up in this study. |
| Clinically significant COPD | Participants with abnormal spirometry, defined as post-bronchodilator FEV ₁ /FVC <0.7 , plus one of the following: 1) FEV ₁ $< 60\%$ predicted or ≥ 1 exacerbation like event within the past 12 months. |
| Mild COPD | Participants with abnormal spirometry, defined as post-bronchodilator FEV ₁ /FVC <0.7 plus both of the following: <ul style="list-style-type: none"> FEV₁ $\geq 60\%$ and No prior history of ECOPD |
| Preserved ratio, impaired spirometry (PRISm) | Participants without spirometrically defined COPD who have post-bronchodilator FEV ₁ $< 80\%$ predicted. |
| Symptomatic non-obstructed (SNO) | Participants without spirometrically defined COPD and without PRISm who have a COPD Assessment Test score ≥ 10 . |

Exploratory analyses to examine the potential impact of SARS CoV-2 infection on the above operating characteristics of the CAPTURE approach will include information in the pandemic and post pandemic period collected from a simple COVID-19 questionnaire that is based on similar questionnaires from other ongoing NHLBI cohort studies.

Longitudinal Follow-up

A pre-defined subgroup of enrolled participants, who meet any of the below criteria will undergo longitudinal follow-up at 12 months,

- Participants with a CAPTURE Score ≥ 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females
- Participants who have abnormal spirometry results, defined as post-bronchodilator FEV₁/FVC < 0.7 or FEV₁ $< 80\%$ predicted at baseline. If a participant is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV₁/FVC is less than 0.65 or FEV₁ is less than 70% predicted, the participant will be considered to have abnormal spirometry for the purpose of follow-up in this study.
- A random sample of approximately 5% who do not meet criteria 1 - 2

Participants who meet the criteria for follow-up will be sent notification shortly after enrollment, and receive reminders at 3, 6, and 9 months. Patient-reported data will be collected by COPD Foundation via telephone, secure web-based server, or mail-based methodologies, based on participant preference.

Subject medical data will be collected from the medical record to assess for changes in practice-level care.

The hypothesis for Aim 3 is that sites where COPD and CAPTURE education and patient-level CAPTURE data are provided to clinicians will exhibit improved COPD diagnosis and COPD-related care compared to sites where COPD education is provided to clinicians.

In exploratory analyses to examine the potential impact of SARS CoV-2 infection on the patient symptoms and health care utilization a simple COVID-19 questionnaire, based on other ongoing NHLBI cohort studies, has been introduced.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Aims 1 and 3

The totality of the published data confirms the clinical and economic impact of undiagnosed COPD, continuing under-diagnosis, and incomplete application of spirometric testing in the primary care community. It suggests that there is value in COPD case-finding that targets COPD patients most likely to benefit from available therapies. These points identify a pressing health care problem that requires an innovative approach to facilitate identifying these individuals. Our preliminary studies enumerated in section 2.2 extend these concepts by demonstrating that:

- Six key domains identify patients with clinically significant COPD.
- Forty-four distinct items resonate with patients and provide important insights for COPD case-finding.
- Five items exhibit excellent sensitivity and specificity in identifying patients with clinically significant COPD.
- PEF provides incremental value in a case-finding strategy.
- The combination of a five-item questionnaire and PEF optimizes a COPD case-finding strategy in English and Spanish speaking patients.

Our proposed study will provide crucial data to address the operating characteristics and clinical translation to our COPD case-finding strategy into the primary care setting. It will also provide an important initial evaluation of the potential clinical impact of the systematic identification of previously undiagnosed COPD patients.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding and respiratory symptoms in primary care is unknown. In exploratory analyses a simple COVID-19 patient questionnaires and additional data elements from medical record review, based on other ongoing NHLBI cohort studies, have been introduced.

Aim 2

The rationale for this aim reflects the importance of establishing if an innovative approach to COPD case finding is considered a pragmatic tool with potential utility for primary care clinicians within real-world clinical practice settings. With the completion of this aim we anticipate confirming that future validated approaches to COPD case finding can be adopted in a broad variety of clinical care settings thereby providing further impetus for the rigorous evaluation of a) case finding guided patient outcomes as part NIH-FDA Clinical Trial Protocol Template – v1.0 7 Apr 2017

of routine primary care clinical practice; b) case finding use in a range of primary care health professional COPD-related education approaches, clinical quality improvement models and diagnostic guidelines; and c) the capacity of clinical case finding and informed follow-up to enhance future COPD clinical care therapeutic paradigms used in primary care practice.

Consistent with Institute of Medicine criteria and US health quality standards for preventive and chronic disease care, the feasibility science qualitative research framework is designed to assist clinical and health education evaluators prepare, assess and evaluate specific implementation factors essential to the success of new diagnostic, therapeutic, educational and programmatic options in real-world clinical practice. This aim's analysis of primary care clinical practice COPD case finding feasibility considerations for CAPTURE includes an initial evaluation of existing COPD diagnostic and case finding processes within the practices, assessment of practices' capacity to change from existing respiratory symptom assessment strategies and an understanding of practice-specific learning preferences associated with new diagnostics and chronic disease diagnosis and management. Patient perceptions of the CAPTURE case-finding process are also obtained to provide a holistic perspective of the clinical feasibility of CAPTURE implementation in primary care practice. Borrowing from the RE-AIM implementation science approach, this aim explores how real-word primary care practices might potentially use CAPTURE to: a) identify target populations (Reach); b) refine current practice appraisal of patient respiratory history, symptoms and diagnostics used to identify clinically significant COPD (Effectiveness/Impact); c) change or integrate COPD case finding into practice workflow (Adoption); d) alter practice communication, education and/or care quality improvement planning for COPD diagnosis and management (Implementation); and e) use COPD case finding consistently over time (Maintenance).

Ten primary care practices will undergo detailed implementation investigation of the CAPTURE case finding model designed to identify patients with COPD most likely to benefit from available therapeutic options. CAPTURE, a one-page questionnaire with selective PEF measurement, is presented to the clinicians of ten practices not participating in aims 1 and 3 as a prospective COPD case finding option awaiting validation. By representing CAPTURE as a model—and not introducing it into actual practice—aim 2 gains recommendation from primary care clinical practice experience with sufficient feasibility generality to circumvent interdependence between the operating characteristic exploration (aim 1) and qualitative feasibility understanding (aim 2) components of our study. The aim 2 results, that include the pooled CAPTURE clinical communication, education and implementation recommendations from real-world primary care practice, are analyzed and applied in concert with local and national research team expertise to enhance the potential impact of CAPTURE's introduction into clinical care in aim 3. Aim 2 results also provide previously unexplored qualitative information necessary for future long-term patient outcome studies of COPD case finding approaches in primary care.

The impact of SARS-CoV-2 infection and its clinical illness, COVID-19, on COPD Case Finding application in primary care is unknown. In a systematic fashion these concepts will be explored during the previously planned follow-up interviews and focus groups with clinical practice and regional PBRN personnel.

4.3 END OF STUDY DEFINITION

Participants that do not meet the criteria for, or are not selected for, longitudinal follow-up will be considered to have completed the study after completion of the baseline visit.

Participants included in the longitudinal follow-up phase will be considered to have completed the study after completion of the Month 12 Assessment as shown in the Schedule of Activities (SoA), Section 1.3.

Clinician participants in aim 2 will have completed the study after participation on their second focus group between months 14 and 16 as shown in the Figure 2, Structure of Aim 2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for Aims 1 and 3

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged 45 – 80 years
4. Able to read and speak English or Spanish

Inclusion criteria for Aim 2

Two Aim 2 practices are selected by each of their 5 affiliated PBRNs based upon willingness to participate and variability of primary care practice type within the PBRN. Differences in practice size, staffing, ownership, prior quality improvement engagement, geography, patient population socioeconomic status (SES) or languages spoken are among the among the selection criteria the PBRNs will utilize to choose.

Clinician participants (10 practices with up to 15 clinicians per practice):

1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with availability and all study procedures for the duration of aim 2 by the 10 practices (through PBRN recruitment) and their up to 15 clinicians within (through informed consent).

Patient participants [200 patients (approximately 40 from each PBRN)] for CAPTURE survey:

1. Provision of signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Male or female, aged 45 – 80 years.

5.2 EXCLUSION CRITERIA

Exclusion criteria for Aims 1 and 3

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Previous clinician provided diagnosis of COPD
2. Treated respiratory infection (with antibiotics and/or systemic steroids) in the past 30 days of baseline
3. Participants unable to perform spirometry due to any of the following conditions within the past 30 days of baseline
 - a) Chest surgery
 - b) Abdominal surgery
 - c) Eye surgery
 - d) Heart attack
 - e) Stroke

Exclusion criteria for Aim 2

1. Clinician participants: current employment at practices participating in aims 1 and/or 3
2. Clinician participants: from practices providing fewer than 2 clinician participants
3. Patient participants: meeting the exclusion criteria for aims 1 and 3 (above)

5.3 SCREEN FAILURES

PBRN coordinators, in conjunction with clinical study site personnel, will pre-screen individuals who are unlikely to be able to complete research spirometry. These individuals will be considered *pre-screen failures*.

Participants who are consented to participate but have a prior clinician diagnosis of COPD will be considered *screen failures*.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention strategies for Aims 1 and 3

Approximately 4800 participants will be recruited from 100 primary care clinics affiliated with six PBRNs. Each PBRN has centrally-based research coordinators with a history of success working in PBRN practices, documented expertise in previous large diagnostic or therapeutic trials, and personnel experienced in recruitment and data collection.

IRB approval will be obtained at each PBRN for approval for patient contact, informed consent and participation in this study.

All patients who meet all inclusion and no exclusion criteria at the participating PBRN clinical site will be eligible for participation. Research coordinators will work with participating practices to identify and approach potential participants. Recruitment strategies may vary depending on the practice.

Enrollment of participants will depend on the gender, ethnic and racial makeup of those that are being recruited from the practices included in this trial. No exclusion criteria apply specifically to women or to minorities. The Data Coordinating Center (DCC) will track enrollment of participants throughout the course of this study. If women and minorities are under-represented in the initial phase of recruitment, a commitment exists to develop recruitment strategies that target these populations so the final study group is a well-balanced representation of the studied population.

Recruitment and retention strategies for Aim 2

Clinician participants: Approximately 150 clinic participants are recruited by: 1) introductory telephone contact with the practice leadership by PBRN research coordinators and the aim 2 research team; 2) follow up letter, time commitment infographic and informed consent forms sent to interested practices outlining aim 2 clinician participant activities and responsibilities; and 3) in-person aim 2 study explanation to clinician participants at the committed practices during the introductory baseline study site visit.

Clinician participant recruitment draws from both prescribing (or “provider”) staff and non-prescribing (or “clinical support”) staff. The aim 2 research team will attempt to obtain an even mix of both clinician staff types from each practice. Retention incentive of clinician participants over 2 years includes provision of on-line COPD education to all clinician participants and monetary incentive to practices as determined by each individual PBRN.

Patient participants: 200 participants (40 from each PBRN) are recruited as a sub-set of the aim 1. Each NIH-FDA Clinical Trial Protocol Template – v1.0 7 Apr 2017

of the 200 patient participants in aim 2 are asked to complete a one-time 10-minute written opinion survey. Their aim 2 participation is concluded at the end of the opinion survey completion.

The aim 2 research team and DCC will track enrollment and retention of all aim 2 participants throughout the course of the 2-year aim 2 study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is applicable to Aims 2 and 3 and consists of healthcare provider education modules.

The practitioners at the 10 sites selected for Aim 2 will receive module 1, Basic COPD education, and may elect to take modules 3-5 for supplemental information on COPD.

For Aim 3, half of the practices will receive Basic COPD education (module 1) and half will receive Basic COPD Education and CAPTURE Education (modules 1 and 2). Practitioners at practices randomized to COPD only education must take module 1 and may elect to take modules 3-5; however, they will not take module 2. Practitioners at practices randomized to COPD+CAPTURE education must take modules 1 and 2, and may elect to take modules 3-5.

1 - Basic COPD Education will be provided in order for providers to optimally manage patients with COPD. The education will incorporate evidence-based recommendations using the 2018 update of the Global Obstructive Lung Disease Strategy(45). For practices enrolled in the pandemic and post pandemic periods, additional information will be provided regarding COPD management in the pandemic era as well as information on steps to maintain patient and staff safety in the clinical sites where CAPTURE patients will be enrolled and assessed.

A 40-minute overview will be presented in the most expeditious manner at each practice site, for example by webinar for all practice personnel over the lunch hour, or audiovisual presentation available on a dedicated CAPTURE web site. The PBRNs have indicated that this module should be no longer than 40 minutes. Topics will include: CAPTURE study description and rationale, importance of COPD in the region of the local practices, COPD definition and diagnosis, patient goals, and management approach. Attendance at this mandatory training will be documented and continuing education credits will be provided for physicians and nurse practitioners by National Jewish Health, an accredited CME provider.

2 - CAPTURE education. An online audiovisual module will be developed to explain CAPTURE interpretation and use in patient evaluation and diagnosis of COPD. This module will only be available to practices randomized to receive the results of CAPTURE for clinical use.

With the information provided in Aim 2 about practice preferences for education, the CAPTURE education module will be revised and made available to practices enrolled in Aim 1 after the completion of Aim 2.

3 - Online advanced COPD education will be available for all practices and continuing education credits will be provided to enhance practitioner participation. Practitioner attendance at each online audiovisual module will be collected including the amount of time spent on each education module, completion of each module with a post-test and evaluation, and CME will be provided. Education will be case-based and will include role playing where appropriate. Seven basic modules of 20 minutes or less will be available both to practices randomized to receive CAPTURE results for clinician use and to control practices that will not receive CAPTURE results and will cover:

1. Diagnosis of COPD: How to diagnose COPD in primary care including medical history, physical exam and role of spirometry, severity categorization
2. Spirometry overview: Basic clinical interpretation
3. Advanced spirometry: Test performance, evaluating quality, advanced case-based interpretation
4. Management overview: Patient goals, smoking cessation, vaccination, patient education, shared decision-making
5. Pharmacotherapy: Inhaled bronchodilators, inhaled corticosteroids
6. Other therapies: Oxygen, pulmonary rehabilitation, surgical approaches
7. Inhalation devices: Patient education

4 – On-site COPD education. Additional funds will be sought to provide on-site COPD education. We have experience in successfully providing half-day on-site education to primary care practices to enhance their management of COPD.

5 – Social media and case conferences. We will use social media (Facebook and Twitter) to provide ongoing education about COPD. Facebook and Twitter posts will provide tips on managing COPD. Online conferences will be scheduled to discuss cases submitted by primary care providers.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

For Aims 1 and 3, this study will use randomization and blinding as two of the cardinal principles of clinical trials to minimize bias.

Randomization. Practices will be randomized into one of the two interventions, COPD education or COPD education + CAPTURE education, in a 1:1 manner, stratified by PBRN. Randomization will occur at the time of site activation and each site will be assigned a unique randomization number. The DCC will prepare the randomization schedule, using computer-generated block randomization with the block size(s) known only by the DCC. A secure web-based application will be built that will be used by the central study coordinators to enter site information (e.g., site ID, stratification factor) and to obtain the randomization number. The information can be printed and sent and/or emailed directly to the study coordinator.

Blinding. This is a single-blind study with the participants blinded to whether their practitioners have received CAPTURE education and patient-level CAPTURE results. Practitioners at sites that are randomized to the control arm (COPD education alone) will be blinded to the CAPTURE questionnaire and PEF results. All practitioners and participants will be blinded to the baseline COPD status of the participants (i.e., blinded to spirometry results), except for safety reasons. In this situation, participants and their clinician will be notified if a participant's post-bronchodilator FEV₁ is less than 30% predicted. For all other participants, they and their practitioners will be blinded to research spirometry results. The coordinator should make every effort to conceal the spirometry results from the participants in these latter cases. Study coordinators should also make every effort to conceal the administration of a post-bronchodilator spirometry test from the practice staff so as not to unblind the physicians to abnormal spirometry.

6.3 STUDY INTERVENTION COMPLIANCE

In practices randomized to share the CAPTURE results with the clinician, the goal is to share results with the clinician at the time of the CAPTURE study visit. Providing results at the time of the clinical visit will allow the clinician to act on the CAPTURE results as soon as possible when the participant is in front of

the clinician. Based on the workflow at each of the practices, this may not always be possible.

Sharing of the CAPTURE results with the participant's primary care clinician will be tracked by the study coordinator enrolling patients at sites randomized to receive CAPTURE results. The sharing of CAPTURE results will be recorded on the study eCRF form. The eCRF will collect the timing of when the results were provided to the practitioner - whether the results were provided to the clinician at the time of the enrollment visit prior to the clinician visit with the patient, or were provided at another time.

If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Tool were sent to the clinician through a HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians.

6.4 CONCOMITANT THERAPY

Practitioners will treat participants using their own clinical judgment. No medications are prohibited. This is not an interventional therapeutic trial.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

In this cluster randomized controlled trial (Aim 3), where practices are the recipients of the intervention and where the interventions are based upon education and access to CAPTURE and PEF results, it is not anticipated that study intervention will be discontinued at the practice level. However, one of the CO-PIs will review safety data, especially SAEs related to baseline spirometry and PEF procedures, to ensure there are no untoward effects of the study on participants.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in Aims 1 and 3 of the study at any time upon request.

Clinician participants in Aim 2 are free to withdraw from participation in the study at any time upon request. If a clinician is no longer working at the participating practice then their involvement in Aim 2 activities will end and no further attempt will be made to include them in the remaining questionnaires or focus groups.

7.3 LOST TO FOLLOW-UP

If a participant selected for longitudinal follow up does not respond to the 12-month questionnaires, coordinators will attempt to contact participants first by the participant's preferred method of communication, either phone or email. At least three attempts will be made. If no response is obtained, the participant's alternate contact method will be attempted three times. Phone calls will be made at different times of the day. If there is no response, a letter will be sent to the participant. If the participant cannot be reached, the alternate contact will be called and/or emailed. If no response is received, a letter will be sent to the alternate contact. If after all of these methods are employed and no

contact with the participant results, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 BASELINE ASSESSMENTS AND DATA COLLECTION

Efficacy data will be collected by patient-reported outcomes and medical record review.

For Aim 1, CAPTURE, PEF results, acute respiratory event history and spirometry will be considered efficacy assessments. They are collected at the baseline visit.

CAPTURE. Participants will complete the 5-item *self-administered* questionnaire and measurement of Peak Expiratory Flow (PEF).

Peak Expiratory Flow (PEF). PEF using the Vitalograph® AsmaPlan® mechanical PEF meter with SafeTway® disposable mouthpieces (Vitalograph LTD, UK) will be measured for all participants. Ideally, PEF should be prior to the participant's physician appointment. The participant will perform three PEF tests. All three measurements will be recorded.

Spirometry. Before spirometry is performed, participants will be asked if they have taken a medicine which they breathed into their lungs from any puffer or inhaler within the past two hours. If participant answers yes, then spirometry will be performed but considered a post-bronchodilator spirometry test. No further spirometry will be needed. If participant answers no, then pre-bronchodilator spirometry will be performed for measurement of forced vital capacity (FVC), forced expiratory volume in one-second (FEV₁), and calculation of FEV₁/FVC (using EasyOne® Spirometer, ndd Medical Technologies Inc., Andover, MA). Testing will be performed in accordance with established American Thoracic Society/European Thoracic Society (ATS/ERS) standards. Local guidelines to minimize risk of SARS-CoV-2 infection will be adhered to, including a minimum of appropriate PPE and infection control techniques.

A Spirometry post-bronchodilator will only be performed if pre-bronchodilator spirometry FEV₁/FVC is less than 0.70 or FEV₁ is less than 80% predicted. Post-bronchodilator spirometry will be performed within 15 to 20 minutes after inhalation of 2 puffs of albuterol 180 mcg HFA using an AeroChamber Plus* Flow-Vu® spacer with one minute between the first and the second inhalation. A separate AeroChamber or comparable spacer, using a one way valve to minimize infectious risk, will be provided for each participant's testing. A standing order for albuterol administration may be used if necessary.

Spirometry is a valid, reproducible means of documenting the presence and severity of airflow limitation. When properly performed with maximum effort and attention to the details of calibration of the instrument, spirometry maneuvers are among the most reproducible of biomedical measures. In the setting of a highly trained, experienced therapist, a coefficient of variation of 2-3% is not unusual. Spirometry will be performed in a standardized manner in accordance with the ATS guidelines, as described in the manual of procedures (MOP). Spirometry is the timed-based measurement of the amount of air that can be forcefully exhaled from the lungs after a full inspiration. In the forced expiratory vital capacity maneuver, a person inhales as big a breath as possible and then blows it out as fast and as long as possible until no more air can leave the lungs. The volume of air leaving the lungs is recorded continuously throughout the maneuver in order to allow calculation of important measures of lung function.

NHANES prediction equations, which are programmed into the Easy On PC spirometers, will be used to

calculate the predicted lung function levels. These require the input of age, height, and race/ethnicity (White, Black, Hispanic). For people of mixed or unknown race the White prediction equations will be used.

PBRN Research Coordinators will be trained and certified in the performance of spirometry testing. Spirometry will be sent for central review for quality control assurance.

Adjudication of the Presence of Obstruction on Post-Bronchodilator Spirometry

The presence of obstruction is determined by the presence of an FEV₁/FVC ratio less than 0.70 after the administration of a bronchodilator. A bronchodilator will be administered to study subjects whose baseline FEV₁/FVC is less than 0.70 or whose FEV₁ is less than 80% of the predicted value.

If a subject is unable to complete a post-bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre-bronchodilator FEV₁/FVC is less than 0.65, the patient will be considered to have COPD for the purpose of follow-up in this study.

Height and weight

Height and weight will be recorded in order to determine appropriate prediction equations for spirometry and possible effect of obesity on spirometry. Height will be recorded and weight will be measured prior to spirometry testing.

Demographic Data Collection

Demographic data including date of birth, gender, ethnicity, race, educational level achieved, daily work schedule, living arrangement and health insurance will be entered into the EDC system.

Contact information including address, phone numbers and email address will be obtained. Alternate contact information will be obtained for two other people, family members not living with the participant or close contacts, who may be knowledgeable about the participant in the event that the participant cannot be contacted for subsequent longitudinal follow-up. Alternate contact information will include name, address, phone numbers and email addresses. All contact information will be stored securely at the clinical site or in a database separate from that developed for the clinical data.

Medical History

Previous medical diagnoses will include comorbidities such as cardiovascular, respiratory and malignant disorders. Influenza vaccination history will also be recorded. This questionnaire will be completed under supervision of the coordinator.

Concomitant Medication Review

Respiratory medications will be recorded at baseline for all participants. This questionnaire will be completed under supervision of the coordinator.

CAPTURE Additional Items Questionnaire

Participants will complete the 13-item *self-administered* questionnaire.

COPD Assessment Test (CAT)

Participants will complete the 8-item *self-administered* questionnaire.

Respiratory symptoms, smoke exposure and exacerbation like events

History of respiratory symptoms and exacerbation like events over the past year as well as smoke exposure (including e-cigarette or equivalent) will be recorded. This questionnaire will be completed

Whenever possible, informed consent, eligibility review, CAPTURE Questionnaire and PEF will be performed prior to the participant's clinic appointment, so that CAPTURE results may be provided to the physician at the time of his/her appointment if the patient is cared for in a clinical center randomized to CAPTURE+ education.

COVID-19 Additional Items Questionnaire

Participants will complete the 18-item *self-administered* questionnaire.

Adverse events

Adverse events related to study procedures will be recorded by the coordinator.

8.2 LONGITUDINAL FOLLOW-UP ASSESSMENTS AND DATA COLLECTION

For Aim 3, the follow-up efficacy assessments are collected from the time of baseline to 12 months in selected cohorts (as described in section 4.1). Medical record abstractions completed by PBRN coordinators and participant questionnaires administered by study team members from the COPD Foundation are used.

Data collected from medical record include:

| | |
|--|--|
| All participants undergoing 12-month follow-up as described in section 4.1 | Current Smokers Only |
| Clinical spirometry ordered or administered | Smoking cessation counseling |
| New recorded clinical diagnosis of COPD | Formal smoking cessation program referral/completion |
| New prescription for respiratory medication (long acting bronchodilator, inhaled steroids) | New prescription for smoking cessation medication |
| Exacerbation like event assessment (hospital, ED, minute clinic, antibiotic/steroid prescription/administration) | Referral to a smoking quit line |
| Vaccination status | |
| Formal pulmonary rehabilitation program referral/completion | |
| Data related to COVID-19 confirmed and suspected cases | |

Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants and administered by COPD Foundation study personnel include:

| | |
|--|--|
| All participants undergoing 12-month follow-up as described in section 4.1 | Current Smokers Only |
| Spirometry referral/completion | Referral to a smoking cessation program |
| New diagnosis of COPD | Referral to a smoking quit line |
| Referral to pulmonologist or other respiratory specialist | New prescription for smoking cessation medication |
| Exacerbation like event assessment | Over-the-counter patches/gum for smoking cessation |
| New prescription for respiratory medication (long acting bronchodilator, inhaled steroids) | |
| CAT score | |
| Attendance of pulmonary rehabilitation | |
| CAPTURE questions | |
| CAPTURE Additional Item Questionnaire | |
| COVID-19 related questions | |

8.3 AIM 2 ASSESSMENTS AND DATA COLLECTION

Practice study introduction and participation confirmation: After PBRN practice selection, the CAPTURE study Aim 2 lead together with the local PBRN Aim 2 coordinator conduct a 15-minute participation confirmation and introduction phone call with the key PBRN contact at each of the two selected practices. The study specifics and timeline are reviewed. After practice participation is confirmed, the on-site practice assessment date is scheduled. Informed consent forms for clinical staff are mailed to each confirmed practice. To reduce practice burden, completed clinical staff informed consent forms (up to 15 clinical staff per practice) can be returned by mail to the University of Michigan School of Public Health office, addressed to Dr. Randall Brown, or saved for completion and picked up at the on-site practice assessment site visit. Following the confirmation phone call, the PBRN Aim 2 coordinator completes a short (15 minute) qualitative questionnaire detailing the selected and confirmed practice demographics and PBRN parameter of practice choice for each of the two practices. The completed PBRN Practice Selection Questionnaire is returned to the Aim 2 data team and stored securely.

On-site Practice Assessment (OSPA): The OSPA is an in-person on-site practice workflow assessment. It includes 2 practice clinicians per practice choice, the PBRN Aim 2 coordinator (if available), the CAPTURE study Aim 2 lead and the CAPTURE Aim 2 research specialist (if the PBRN Aim 2 coordinator is not present). The objective of the visit is to detail specifics of practice workflow, practice physical characteristics, staff roles, clinical information gathering patterns for respiratory patients, electronic health record communication, continuing education structure, and quality improvement structure. The assessment takes place in three parts; the pre-observation practice overview (conducted with the 2 practice clinicians – 60 minutes), the ½ day practice workflow observation (observation by one member

of the Aim 2 research team of common and testing areas used for the respiratory patient). There is no patient engagement and no collection of patient-specific identification or health information), and the post-observation practice summary (conducted with the same 2 practice clinicians – 30 minutes).

The 3 OSPA assessment tools are:

- i) The Pre-workflow Observation Practice Assessment Review Questionnaire
- ii) Respiratory Workflow Assessment Review
- iii) The Post-workflow Observation Practice Assessment Review Questionnaire

Also at the OSPA, informed consent is obtained from all remaining participating staff (up to 15 clinical staff per practice) by the CAPTURE Aim 2 team and returned to the Aim 2 data team for secure storage.

Clinical Staff Questionnaires (Baseline/6/12 months). Written or on-line questionnaires are provided to participating and consented staff personnel at two practice levels -- Non-Prescribing clinical (also known as “support”) staff and Prescribing (PR) clinical (also known as “provider”) staff.

Non-Prescribing (NPR) clinical staff are clinical practice personnel involved in clinical workflow (including registered nurses, licensed practical nurses, medical assistants, medical assistants and receptionists), yet not having the role to make final and official medical diagnostic and management disposition plan decisions for and with patients. Prescribing (PR) clinical staff are prescribing clinical practice personnel involved in clinical workflow (including doctors, nurse practitioners, and physician assistants) who may independently make final medical diagnostic and management disposition plan decisions for and with patients.

Questionnaire items explore clinician demographics, including past education, duration of current employment and currently held clinical position. COPD knowledge, attitudes, beliefs, practice patterns and self-efficacy regarding COPD diagnosis, management, spirometry testing and interpretation, practice workflow and communication in the clinical primary practice care of adult patients with respiratory disease. Additional questions include preferred continuing education method and clinical staff quality improvement modalities for respiratory disease management. Specific examples of past practice chronic disease diagnostic changes and the individual and practice-wide levers of success and challenge associated with those changes are explored.

Each of the 3 (baseline, 6-month and 12-month) questionnaires are completed within 30 minutes. No identifying patient data is collected. Online questionnaires are collected and secured by the CAPTURE DCC and Aim 2 research team. The participants who complete written questionnaires (per their preference) mail completed questionnaires via pre-addressed stamped envelope to the CAPTURE DCC and Aim 2 research team.

Patient Opinion Surveys:

200 patient participants, 40 from each PBRN, are recruited as a sub-sample from Aim 1 practices. Patient participants fulfill all inclusion and exclusion criteria and receive informed consent for survey participation as part of aim 1.

Eligible participants complete a written one-time 5 to 10 minute CAPTURE opinion survey. Patient survey data is collected by Aim 1 research coordinators and is processed with Aim 1 baseline patient data. Patients receive a \$15 gift card for completion of the survey Aim 2 patient participation ends at the completion on the lone opinion survey.

Participants who prefer to complete the 5 to 10-minute survey online via Qualtrics will be sent a secure, Qualtrics link via email. The Qualtrics survey will include a brief, introductory screen affirming consent, describing the survey and instructions about participation. Once the survey is complete, participants will

see a screen with instructions about how to obtain their \$15 gift card and how to contact study staff with questions regarding the survey.

Modular online COPD education. Access to free, COPD on-line, continuing education is provided for all clinical staff at each practice. Each module will take 20 minutes or less. Modular components of and access to COPD education is described in the protocol. Aim 2 clinician participant access and completion of COPD education modules is assessed by clinician questionnaires and focus group item response over 12 months (between months 2 and 14 of Aim 2 timeline).

COPD in Primary Care/CAPTURE Introduction Focus Groups:

Two 45 to 60-minute focus group discussions occur at each Aim 2 practice. Focus groups are informed by practice demographics, practice assessment data – including respiratory workflow, baseline clinical staff questionnaire data regarding respiratory knowledge, attitudes, beliefs and practice preference for the diagnosis and care of adult patients with respiratory disease as well as patient opinion from CAPTURE surveys and past CAPTURE study (46, 47). Focus group candidate themes and prompts are developed for non-prescribing clinical staff (NPR) and prescribing clinical staff (PR) and are presented at separate on-site focus group sessions to allow more detailed discussion of role responsibility in the context of daily practice workflow, generating a more abundant qualitative data sample. Separation of and PR clinical staffing implementation themes into two focus groups also limits potential for hierarchical work-related discussion suppression described in other short duration focus group studies (48-52).

The focus group moderator introduces the CAPTURE tool utilizing CAPTURE education components described in Section 6.1.1. The focus group moderator follows RE-AIM prompts for CAPTURE implementation planning discussion throughout the focus group. Targeted COPD self-efficacy limitation themes from questionnaire data (including awareness and/or use of validated respiratory assessment questionnaires, spirometry, COPD guidelines, inhaled medication patient education, oxygen therapy, smoking cessation education, vaccination recommendation, pulmonology specialty care and pulmonary rehabilitation referral) are explored. Questions will probe clinicians to identify and explain levers that may maximize uptake of CAPTURE use in their practices as well as potential barriers to implementation. The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis and CAPTURE intra-office clinical communication and COPD/CAPTURE education preference assessment. Additional codes will be developed for sub-themes and emergent themes.

Development of Practice-Based CAPTURE Implementation PBL Cases:

From analyses of the 2 NPR and 2 PR CAPTURE Introduction focus groups per PBRN, baseline clinical staff questionnaire data, online CAPTURE opinion surveys, and on-site practice assessments, 1 primary care practice CAPTURE implementation case per PBRN (total implementation cases = 5) is created by the Aim 2 research team. Given local knowledge of chronic disease management quality improvement history, effort, challenge and successes, each PBRN's participation in case creation will be instrumental. The Aim 2 research team will lead case creation using evidence-based problem based learning (PBL) techniques (53-57). The Center for Research on Learning and Teaching (CRLT) at the University of Michigan will serve as research reference for PBL case development qualification (58). Each local PBRN PBL case will be distributed to the Aim 2 clinical staff at the 2 participating PBRN practices 2 weeks prior

to the CAPTURE Implementation focus groups, giving Aim 2 participants an opportunity to read the case introductions prior to the focus group session. Also, each practice will receive one additional non-PBRN case for focus group discussion as selected by the Aim 2 research team. Therein, each of the 5 CAPTURE implementation PBL cases will receive 2 comprehensive focus group reviews (see below).

CAPTURE Implementation PBL Case Presentation Focus Groups:

Each practice participates in a final pooled (NPRs and PRs together) on-site focus group. Two CAPTURE implementation cases (described above) are discussed at each focus group. The focus will explore, discuss, glean and create optimal 1) CAPTURE implementation, 2) CAPTURE clinical communication, 3) CAPTURE/COPD education and 4) CAPTURE primary care quality improvement recommendations pooled from all clinical practice levels for each of the 2 presented cases.

The Aim 2 research team will record each focus group using audio and written note-taking that will allow an abridged yet detailed tape-based micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions. Key themes informing consensus discussion, program modifications and key elements of the CAPTURE RE-AIM implementation dimensions will be identified. Audio-recordings will be professionally transcribed and codes will be generated for the interview topics and key research questions. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Additional codes will be developed for sub-themes and emergent themes.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.4.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AEs.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.4.2.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.2.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events (AE)s that occur during the baseline visit will be recorded.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.4.4 ADVERSE EVENT REPORTING

All AEs that occur at baseline visit will be recorded in the case report form and reported to the DCC. We anticipate few adverse events due to the non-invasive nature of the study procedures. Participants will only be enrolled if they meet the study eligibility criteria, including assessment for contraindications for NIH-FDA Clinical Trial Protocol Template – v1.0 7 Apr 2017

spirometry. Targeted safety questions will be asked of all patient participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities.

8.4.5 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB at the institution where the event occurred and the University of Michigan IRB will be notified of any serious adverse experience within 7 calendar days of occurrence. These will be reported to the DSMB.

Follow-up of serious adverse events

All SAEs will be followed up until resolution or permanent outcome of the event. All follow-up information will be included in the case report form. The DSMB will make recommendations to ensure data integrity and the safety of study participants.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC within 7 calendar days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC within 14 calendar days of the

investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB (physicians with the appropriate expertise, including non-involved pulmonologists, primary care physicians, and independent statisticians with clinical experience). Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the Principal Investigators.

9 STATISTICAL AND ANALYTICAL PLANS

9.1 SAMPLE SIZE AND POWER

9.1.1 PRIMARY OBJECTIVES

Define the sensitivity and specificity of CAPTURE for identifying previously undiagnosed patients with clinically significant COPD in a broad range of primary care settings. We will also explore clinical practice implementation approaches to and acceptance of CAPTURE case finding for clinically significant COPD in a range of primary care practices. Further, we will define the impact of CAPTURE information provided to clinicians in identifying and managing patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings.

9.1.1.1 SENSITIVITY AND SPECIFICITY OF THE CAPTURE TOOL

Primary Hypothesis 1. The CAPTURE tool will exhibit excellent sensitivity and specificity in diagnosing clinically significant COPD as defined by post-bronchodilator FEV₁/FVC < 0.70 in addition to either ≥1 exacerbation-like event (ECOPD) within the past 12 months or an FEV₁ < 60% predicted. Approximately 5000 patients will be enrolled in the study with the expectation that 300-800 of these will have previously undiagnosed clinically significant COPD, identified through research spirometry and documentation of prior respiratory events. Amongst cases, we will calculate the proportion of individuals who are at high risk for clinically significant COPD based on CAPTURE (sensitivity). Similarly, amongst non-cases, we will calculate the proportion of individuals not classified as having clinically significant COPD based on CAPTURE (specificity). Corresponding 95% confidence intervals will be calculated.

Based on our preliminary data drawn from a research setting, we noted 89.7% sensitivity and 93.1% specificity for CAPTURE. Table 9-1 shows the range of sensitivity and specificity 95% confidence interval widths that would result if the true sensitivity or specificity is 85%, 90% or 95% across a range of sample sizes. For instance, if we find 500 individuals with confirmed clinically significant COPD and CAPTURE has 90% sensitivity, then the 95% confidence interval for sensitivity would be 90% ± 2.6%. Similarly, if 4,000 individuals are confirmed to have no evidence of clinically significant COPD and CAPTURE has 90% specificity, then the 95% confidence interval for specificity would be 90% ± 0.9%.

| | | Sensitivity or Specificity | | |
|-------------|--|----------------------------|--------|--------|
| Sample Size | | 85% | 90% | 95% |
| 5000 | | ± 1.0% | ± 0.8% | ± 0.6% |
| 4000 | | ± 1.1% | ± 0.9% | ± 0.7% |
| 1000 | | ± 2.2% | ± 1.9% | ± 1.4% |
| 500 | | ± 3.1% | ± 2.6% | ± 1.9% |
| 250 | | ± 4.4% | ± 3.7% | ± 2.7% |
| 100 | | ± 7.0% | ± 5.9% | ± 4.3% |
| 50 | | ± 9.9% | ± 8.3% | ± 6.0% |

9.1.1.2 ADOPTION AND IMPLEMENTATION OF THE CAPTURE TOOL IN PRIMARY CARE PRACTICE

Primary Hypothesis 2: *A COPD case finding methodology using a validated one-page, five-item questionnaire with selective PEF measurement (CAPTURE) can be incorporated into the clinical practice patterns, clinical workflow, communication and practice-based quality improvement paradigms of a variety of primary care clinical settings.*

Aim 2 is a qualitative study to determine the efficacy of workflow integration of the CAPTURE tool. Statistical analysis of the clinician questionnaire will involve simple sums of each item and reviewing answers across practices and region. Standard frequencies for questions will be developed to examine patterns in responses.

The clinician focus groups will be conducted on-site at each practice at a time convenient for the participating clinicians. The number of prescribing and non-prescribing clinicians will equal 15 per practice and is based on interest with a maximum of 8 prescribing clinicians/practice. The sample size will follow a basic qualitative sampling standard of interviewing to redundancy or saturation. The number of clinicians to be interviewed (up to n=15 in each practice) is estimated based on achieving concept saturation. Reflecting regional primary care practice norms and to bolster concept saturation, PBRN Aim 2 coordinator focus group discussion participation is encouraged for very small practices where the participating prescribing and non-prescribing clinician total is less than or equal to 4. For all practice focus groups questions will explore the described Aim 2 CAPTURE RE-AIM concepts, barriers to implementation of the CAPTURE tool at other practice sites, standard processes for COPD and respiratory care diagnosis and management for each clinical role within the practice, and perception of quality improvement methods at each practice. Clinician focus groups are conducted on-site at each of the 10 practices.

Transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to

capture significant changes in participants' attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with our Aim 2 research team and will inform the development of the case studies for the latter part of the project.

9.1.1.3 PRACTICE BEHAVIOR IN SITES WITH VERSUS WITHOUT CAPTURE EDUCATION AND PATIENT LEVEL CAPTURE DATA PROVIDED

Primary Hypothesis 3: *Sites where basic COPD and CAPTURE education are provided to clinicians, along with patient level CAPTURE data, will have a higher probability than control sites (i.e., those receiving only basic COPD education) of meeting the composite endpoint in their CAPTURE+ patients within 12 months of baseline.* From medical record review and follow-up patient survey responses, the composite endpoint is met if one of the following is recorded: (1) referral for or completion of clinical spirometry testing, 2) new clinical diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), 4) referral to a specialist for respiratory evaluation/ treatment, or 5) referral for or completion of pulmonary rehabilitation.

The study will enroll 50 CAPTURE practices and 50 control practices; each practice will enroll 50 patients (for a total of approximately 5,000 patients). We project that within each practice, there will be at least 5 patients previously undiagnosed with COPD who have a CAPTURE+ screening result. The primary analysis will be to compare the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in the two intervention arms. For power and sample sizes computations, this is a cluster randomized trial of n=50 clusters (practices) per intervention arm with 5 CAPTURE+ patients per cluster (practice). The primary power calculation is based on comparing the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Table 9-2 displays power for a two-sample test comparing average cluster sample proportions, accounting for possible intra-cluster correlation coefficient (ICC) values of 0.05, 0.10 and 0.15 that are typically seen in cluster randomized trials of behavioral interventions (<https://www.abdn.ac.uk/hsru/research/research-tools/study-design/>). These calculations assume a type I error of 5% and that the control arm meets the composite endpoint in 5% of CAPTURE+ patients and the CAPTURE arm meets the composite endpoint in higher percentages (columns of Table 9-2). There will be variability in the actual number of CAPTURE+ patients per practice. It is standard practice to inflate the number of needed clusters by 12% to account for this extra source of variability. Therefore, our power calculations are based on 44 clusters per intervention arm.

Table 9-2. Overall power to detect a difference in rate of meeting primary endpoint in CAPTURE group (50 practices/clusters) vs usual care (50 practices/clusters), assuming 5% performance rate in usual care; 50 patients total / practice; assuming 10% prevalence gives 5 CAPTURE+/practice

| Improvement over usual care | +7.5% | +10% | +15% | +25% | +50% |
|-----------------------------|-------|------|------|-------|-------|
| ICC=0.05 | 0.72 | 0.89 | 0.99 | >0.99 | >0.99 |
| ICC=0.10 | 0.65 | 0.84 | 0.98 | >0.99 | >0.99 |
| ICC=0.15 | 0.59 | 0.79 | 0.97 | >0.99 | >0.99 |

9.1.2 SECONDARY OBJECTIVES

9.1.2.1 SENSITIVITY AND SPECIFICITY IN PREDEFINED SUBGROUPS

| Table 9-3. Projected numbers of clinically significant COPD cases and non-cases we expect by subgroup of interest assuming prevalence of obstructed individuals is between 6-16%. (*Non-Hispanic) This table assumes prevalence of non-clinically significant COPD similar to clinically significant COPD (not included in this table). | | | | | | | | | | |
|--|-------------|-------------|-------------|--------------|--------------|----------------|-------------|-------------|--------------------|---------------------|
| | Total | Men (50%) | Women (50%) | White* (62%) | Black* (15%) | Hispanic (18%) | Rural (46%) | Urban (54%) | Ever-Smokers (40%) | Never-smokers (60%) |
| Projected # confirmed clinically significant COPD by subgroup | 300-800 | 150-400 | 150-400 | 186-496 | 45-120 | 54-144 | 138-368 | 162-432 | 120-320 | 180-480 |
| Projected # confirmed no COPD by subgroup | 3,400-4,400 | 1,700-2,200 | 1,700-2,200 | 2,108-2,728 | 510-660 | 612-792 | 1,564-2,024 | 1,836-2,376 | 1,360-1,760 | 2,040-2,640 |

We will also examine several subgroups of interest that are key to addressing our overall goal of defining the value of CAPTURE across a broad range on individuals. These will include sex, ethnic groups, rural and urban location, and educational level, among individuals with clinically significant COPD, spirometrically defined COPD and individuals with “mild” COPD as defined in this protocol. We have specifically chosen clinical sites with a diverse gender, racial and ethnic mix, and rural and urban mix with the expected prevalence of clinically significant COPD cases and controls by subgroup outlined in Table 9-3, again with corresponding sensitivity and specificity confidence interval widths in Table 9-1. For example, if sensitivity of CAPTURE in Hispanic individuals is 90%, then a sample size of approximately 100 would give a confidence interval of $90\% \pm 5.9\%$. We believe that with an overall sample size of 5,000 recruited patients we will have adequately sized subgroups to assess the operating characteristics of CAPTURE in the subgroups of interest.

9.1.2.2 FURTHER ANALYSIS OF ASSOCIATIONS BETWEEN MEETING COMPOSITE ENDPOINT AND INDIVIDUAL AND PRACTICE LEVEL OUTCOMES

Secondary analyses for evaluating practice behavior are exploratory, and therefore not included in a formal power and sample size analysis. These analyses are described further in Section 9.3.2.

9.2 POPULATIONS FOR ANALYSES

Aim 1

Population used for sensitivity calculations are all enrolled patients with clinically significant COPD as defined by post-bronchodilator $FEV_1/FVC < 0.70$ in addition to either ≥ 1 exacerbation-like event (ECOPD) within the past 12 months or an $FEV_1 < 60\%$ predicted.

Population used for specificity calculations are all enrolled patients with no demonstrable COPD as determined by research spirometry conducted upon study entry, $FEV_1/FVC \geq 0.70$.

Aim 2

Clinician participants: enrolled clinicians are from 2 primary care practices in each of five US PBRN regions that do not engage in Aims 1 or 3 investigation. Eligible clinicians include primary care providers and primary care clinical non-provider support personnel.

Patient participants: enrolled as a sub-sample of Aim 1 participants at baseline. One CAPTURE patient opinion survey is administered at baseline. Aim 2 participants fulfill the inclusion, exclusion and population analysis criteria of aim 1.

Aim 3

Populations used in 2-sample comparisons of outcomes between the two intervention arms will be based on randomization group (intent-to-treat analysis).

For primary analysis of each Aim 3 outcome, the analysis population will consist of all patients with follow-up data for that outcome from both the medical record review and the patient survey administered by the COPD Foundation (section 8.2).

Secondary analyses will be performed using alternative analysis populations, including

1. All patients with outcome data from the medical record review, and
2. All patients selected for follow-up.

9.3 STATISTICAL ANALYSES

9.3.1 SENSITIVITY AND SPECIFICITY (AIM 1)

SAS version 9.4 PROC LOGISTIC will be used for computations. Calculations of sensitivity and specificity along with their corresponding 95% confidence intervals assume independent Bernoulli outcomes for each patient. Clinically significant COPD+ and COPD- populations selected for these analyses are described in Section 9.2. CAPTURE+ patients are those with a baseline CAPTURE score ≥ 5 or with a baseline CAPTURE score of 2, 3, or 4 with a low PEF (defined as <350 L/min for males, <250 L/min for females).

In addition to the primary sensitivity/specificity calculations, sensitivity/specificity and associated 95% confidence intervals will be calculated in predefined subgroups: sex, ethnic subgroups, rural and urban location, and educational status. As part of secondary analyses, receiver operating characteristic (ROC) curve analyses will evaluate different thresholds of the CAPTURE questionnaire score in defining a positive clinically significant + COPD screen, separately and in combination with low PEF characteristics, **and the additional CAPTURE questions**. As part of this exploration, participant and practice level data as well as interactions with the CAPTURE tool results, will be considered as predictors of clinically significant COPD using multivariable logistic regression. Corresponding positive and negative predictive values will be estimated across the range of prevalence percentages seen at the enrolled practices. Model selection in secondary logistic regression analyses will be based on forward selection using maximum likelihood theory, with entry into the model dependent on statistical significance at the 0.05 level. Exploration of this nature has the potential to produce artificially high operating characteristics (area under the curve [AUC], sensitivity and specificity) based on overfitting the data. SAS 9.4 PROC LOGISTIC includes a cross-validation approach to ROC curve analysis [ROCOPTIONS(CROSSVALIDATE)] that we will use when assessing operating characteristics for any new prediction tool that goes beyond the original CAPTURE metric considered in primary analyses. Once a final logistic regression model has been selected, classification thresholds for predicting clinically significant COPD will be described by the investigative team from the cross-validated ROC curve. Calibration plots of observed versus predicted sensitivity, and observed versus predicted specificity, will be conducted across previously specified subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

All of the above analyses will be applied to these additional populations: (1) patients with spirometrically defined COPD and (2) patients with mild COPD.

9.3.2 PRACTICE BEHAVIOR (AIM 3)

The primary analysis of the Aim 3 primary endpoint will be to compare the average cluster sample proportion (average proportion of CAPTURE+ patients per practice meeting composite endpoint) between intervention arms. Practices that do not identify any CAPTURE+ subjects will not contribute to the primary analysis. The primary analysis is a two-sample test comparing average cluster sample proportions that explicitly takes into account correlation between individuals treated within the same practice. A two-sided p-value < 0.05 will be considered statistically significant. This analysis corresponds to a generalized estimating equation (GEE) regression analysis with (1) individual-level binary composite outcome data, (2) CAPTURE intervention group as a covariate, (3) practice id used to identify correlated outcomes, (4) exchangeable correlation matrix that assumes similar correlation between all composite outcome results for patients within the same practice, and (5) an identity link function so that the coefficient parameter corresponding to CAPTURE intervention group represents a difference in outcome probability. The primary analysis would then correspond to a test for whether the CAPTURE intervention group parameter is non-zero. There are no planned interim analyses for the primary endpoint, the rationale being that this is not a pharmaceutical or device trial that would benefit from standard stopping rules for efficacy. A DSMB will be monitoring the study for safety and study integrity.

Secondary analyses on meeting the composite outcome for participants who are CAPTURE+ will employ the GEE analysis framework with individual and practice level predictors in addition to the CAPTURE intervention group. Interactions will be assessed. We will also use the GEE framework to study and describe each of the individual components of the composite outcome as they relate to individual and practice level outcomes. In the subset of smoking patients, we will use GEE regression analysis to study additional binary outcomes, such as incidence of physician counselling/recommendation to stop smoking, physician referral to a formal smoking cessation program, newly prescribed smoking cessation medication, and referral to a smoking quit line.

For each Aim 3 outcome that is collected via both medical record review and patient survey, the primary analysis will be among patients with complete outcome data from both the medical record and patient survey. Sensitivity analyses will be conducted by imputing missing outcome data using different assumptions and applying the primary analysis method to the resulting data sets. Sensitivity analyses will include (1) imputation of negative responses (i.e., responses indicating that the outcome has not occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review data; (2) imputation of positive responses (i.e., responses indicating that the outcome has occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review data; and (3) multiple imputation of all missing outcome data using the observed outcomes and covariates, followed by analysis of all patients selected for follow-up.

In participants who are CAPTURE+, change in CAT score will be analyzed using mixed models with a random effect for practice. The average cluster sample proportion of patients who experience exacerbations will be compared between intervention groups using methodology similar to that used for the primary endpoint. Subject to having sufficient mortality events, survival analysis allowing for correlation of endpoints within cluster (practice) will be used to compare mortality between

intervention groups and perform multivariable analysis. We will explore differences between intervention groups in the average cluster sample rate of hospitalizations again using GEE. All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD, Mild COPD, PRISM, and symptomatic non-obstruction. Practices that do not have any patients with these conditions will not contribute to analyses of these secondary endpoints, respectively.

Model selection in GEE secondary analyses will be based on statistical significance at the 0.05 level using robust sandwich estimation of variability within clusters. Model fit will be checked by comparing observed versus predicted values within predefined subgroups of interest (sex, ethnic subgroups, rural and urban location, and educational status).

Analyses will be repeated in populations separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic.

9.3.3 CAPTURE IMPLEMENTATION RECOMMENDATIONS (AIM 2)

Site-specific practice information, clinician knowledge and behavioral questionnaires, as well as patient opinion survey responses are recorded primarily to populate focus group themes for qualitative analysis. Secondary analyses of individual clinician and patient response using frequencies, means, ranking and dispersion by clinician type, practice and PBRN is accomplished using SAS version 9.4. Correlation with implementation recommendation is determined using GEE variance models.

Audio transcripts of clinician focus groups will all be digital and entered into a qualitative data analysis program, NVivo for Mac. This program allows for an investigation of the salience, patterning, and contexts of key discourse items. Grounded theory methods will be used to identify and label recurrent themes and concepts within textual materials. Texts will be examined line-by-line, key phrases assigned tentative category labels, and coded passages grouped under the themes of feasibility, barrier and utility. The analyses will look for “traces” in dialogue, including repetitions, key words, evaluation statements, and metaphors. Micro-interlocutor analysis of focus group emergent themes, questions, answers and interactions will account for individual gaps in focus group participation. Change in salience, patterning, or content of key themes will provide further empirical evidence regarding the efficacy of our program’s efforts to impact clinician community norms and behaviors. An audit trail will be maintained to document the position of text material from which codes and themes are developed. We will use word/code counts of repetitive themes and concepts to indicate patterns. By allowing for open-ended responses, the narratives and notes will allow us to capture significant changes in participants’ attitudes or behaviors. Codes and themes will be discussed iteratively with the research team members to hone definitions and assure consistency of interpretation. We will establish a coding dictionary and all interviews will be coded using the complete set of themes. Reviewing the transcripts line-by-line, all substantive information will be assigned a priori codes as relevant for CAPTURE RE-AIM implementation planning, COPD diagnosis, CAPTURE intra-office clinical communication, and COPD and CAPTURE education preference, and COPD diagnosis quality improvement assessment. Two independent coders will code each document to assure inter-coder reliability. Preliminary results will be shared with the Aim 2 data team and will inform the development of the CAPTURE case studies and primary care practice implementation recommendations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise.

A HIPPA waiver will be submitted to each IRB to prescreen clinic schedules and patient panels for recruitment purposes. The PHI reviewed by the coordinator in the electronic health record (EHR) will include age, date of birth, diagnosis of COPD, respiratory medications, and other medical conditions that are contraindicated for spirometry. A waiver of written consent will be submitted to each IRB to pre-screen potential participants for eligibility criteria prior to informed consent. The pre-screening will either be by telephone prior to an upcoming clinic visit, or in person at the time of the visit. An IRB-approved telephone/in-person screening script will be submitted to each IRB.

A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will additionally have the opportunity to review the study and informed consent prior to providing consent for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All PBRN research coordinators, COPD Foundation study staff and other clinical investigators will be certified by their local IRB in informed consent and human studies research.

Clinicians interested in participating in the qualitative, minimal risk study for Aim 2, will be given the opportunity to review the consent form below and sign it. This can happen once their practice agrees to participate in Aim 2 activities or during the first in person site visit with Dr. Brown.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator

(PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with COPD Foundation study team access to aid in contacting participants at the 12-month follow-up. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

For the online Aim 2 patient opinion survey, Qualtrics is used. Qualtrics is a secure University of Michigan (U-M) contracted-for cloud service that can be used to maintain or share the university's sensitive unregulated data, as well as some kinds of sensitive regulated data.

U-M's agreement with Qualtrics includes a Business Associate Agreement. This means individuals may use this service to maintain Protected Health Information (PHI) regulated by HIPAA. Complying with HIPAA's requirements is a *shared responsibility*. Users sharing and storing PHI in Qualtrics are responsible for complying with HIPAA safeguards, including:

- Using and disclosing only the minimum necessary PHI for the intended purpose.
- Obtaining all required authorizations for using and disclosing PHI.
- Ensuring that PHI is seen only by those who are authorized to see it.

- Obtaining all necessary data-sharing agreements and Business Associate Agreements for using and disclosing PHI.
- Following any additional steps required by your unit to comply with HIPAA.

Sensitive data, including PHI, may be collected and stored in Qualtrics for non-clinical, academic purposes only (for example, research and hospital quality improvement initiatives). Qualtrics cannot be used for any clinical applications, no matter the sensitivity level of the data

11 STUDY ADMINISTRATION AND OVERSIGHT

11.1 STUDY LEADERSHIP

11.1.1 PRINCIPAL INVESTIGATORS

The principal investigators are responsible for providing direction and oversight of all study activities.

| Principal Investigators | |
|--------------------------------|----------------------------|
| Fernando Martinez, MD, MS | MeiLan Han, MD, MS |
| Weill Cornell Medicine | University of Michigan |
| 1305 York Avenue, | 1500 E. Medical Center Dr. |
| Box 96, Room Y-1059 | 3916 Taubman Center |
| New York NY 10021 | Ann Arbor, MI 48109 |
| 646-962-2748 | 734-936-5201 |
| Fjm2003@med.cornell.edu | mrking@med.umich.edu |

11.1.2 PRACTICE BASED RESEARCH NETWORKS (PBRN)

PBRNs will have the following roles and responsibilities:

CAPTURE Study Preparation

1. Review protocol to help identify operational details
2. Submit final protocol and informed consents to all IRBs necessary for the participating sites
3. Complete and maintain current human participants training for all main study personnel as required by the IRB
4. Attendance of PBRN coordinators at in person training, spirometry certification for all coordinators, update of spirometry quality assessments and training
5. Identify and recruit local practice sites to participate in the study

CAPTURE Study Implementation

1. Facilitate COPD and when appropriate CAPTURE education
2. Maintain regular contact with participating PBRN practice sites during their period of patient enrollment
3. Supervise and send PBRN Research Coordinators to enroll patients, perform study visits including completion of the CAPTURE questions, peak flow, spirometry, and collect other information on all enrolled patients
4. Complete pre bronchodilator spirometry on all participants
5. Complete post bronchodilator spirometry on participants with abnormal pre-bronchodilator spirometry as defined by study algorithm (e.g. those with pre bronchodilator results consistent with

obstruction)

6. Facilitate completion of data entry to the data coordinating center
7. Follow up by research coordinator for patients failing to respond to the follow up questionnaires
8. Collect practice outcome data related to enrolled patients at close of study from either electronic medical records or if practice does not have EMR, by manual record review

Patient participants and staff participants will be recruited from the PBRNs.

| PBRN | Location | Director |
|---|--------------------------|---|
| Atrium Health | North Carolina | Hazel Tapp, PhD |
| LA Net Community Health Network | Southern California | Lyndee Knox, PhD |
| High Plains Network | Colorado | Linda Zittleman, MD |
| Duke Primary Care Research Consortium Oregon Rural Practice-Based Research Network | North Carolina Oregon | Rowena Dolor, MD Nancy Elder, MD |
| University of Illinois, Chicago | Illinois | Min Joo, MD |
| Circuit Clinical, Buffalo | New York | Irfan Khan, MD |

11.1.3 SPIROMETRY CORE

Led by Dr. David Mannino, the Spirometry Core will maintain quality of the research spirometry that is integral to the success of the study. The work will be done in conjunction with a research assistant. This includes the following functions:

1. Development of the operation manual for the sites
2. Training of the site staff in the use of the spirometry equipment (including travel to training and sites as needed)
3. Certification of staff in spirometry
4. Assessing staff adherence to protocols for the use of bronchodilators
5. Grading and adjudication of spirometry
6. Importing processed spirometry into spreadsheets
7. Uploading processed data to data coordinating center
8. Working with data coordinating center to verify and clean data

In addition, Dr. Mannino will be a critical part of the team that evaluates the data both from spirometry and the other components of this study (the CAPTURE tool, quality of life measures, etc.), in addition to being part of the writing team that analyzes data and disseminates the findings from this study.

11.1.4 IMPLEMENTATION CORE

Dr. Randall Brown will lead the qualitative Aim 2 activities which assess the implementation strategy and acceptance recommendations for CAPTURE use in primary care practice. His team includes an Aim 2 project manager and dedicated research assistant. Led by Dr. Brown the Aim 2 team coordinates with PBRNs and their selected Aim 2 practices and will conduct qualitative site visits and focus groups in addition to administering clinical practice behavioral questionnaires. Drs. Barbara Yawn, Barry Make, Bruce Bender and Julia Houfek will contribute to the development of the web based educational modules and the qualitative efforts on this project.

11.1.5 DATA COORDINATING CENTER (DCC)

Dr. Cathie Spino directs the DCC, housed at the University of Michigan within the Statistical Analysis of Biomedical & Educational Research (SABER) Unit of the Department of Biostatistics in the School of Public Health. The DCC staff will include a Database programmer, Data manager, Senior Unblinded Statistician, Statistical Analyst, Project Manager, Clinical Monitor, Web Programmer/Designer, and a Research Administrator. In addition, the blinded senior statistician, Dr. Susan Murray, is located at the University of Michigan. The DCC plays a pivotal role in the design, implementation, execution and administration of the study. The DCC will be responsible for randomization, eCRFs and online reporting systems, preparation of the manual of operations for data entry, addressing questions regarding entry and analysis, monitoring recruitment, follow-up and adherence to protocol, and scheduling and arranging meetings of the Executive Committee, Steering Committee, and Medical Monitor. The DCC will prepare all of the routine study reports for the Executive Committee, Operations Committee, and Medical Monitor. The DCC will interact with all of the Cores and other Committees, as needed. The DCC will compile data tables and listing for DSMB reports.

11.1.6 CLINICAL COORDINATING CENTER

The Clinical Coordinating Center (CCC) will be led by Principal Investigators Fernando Martinez, MD, MS at Weill Cornell Medicine, and MeiLan Han, MD, MS at the University of Michigan. Dr. Martinez will be responsible for overall study oversight as well as fiscal management of the overall project and capitation payments to sites for work performed. He will also be responsible for communication with NIH and submission of annual reports. Dr. Han will work with the Data Coordinating Center to oversee clinical trial enrollment and, along with her statistical team, be responsible for coordinating statistical analysis. The process for making decisions on scientific direction and allocation of resources will be made by both Drs. Martinez and Han, with input from the rest of the investigative team as needed.

Additional Clinical Coordinating Center (CCC) responsibilities:

- Establish subcontracts with enrolling sites, central laboratories, imaging service providers, and others as appropriate
- Protocol development and scientific design oversight
- Statistical analysis
- Participating study site selection
- Review of serious adverse events and unanticipated problems involving risk to participants or others, reporting to participating centers and regulatory reporting
- Prepare and maintain Clinical Coordinating Center IRB submissions
- Analyze and present data to DSMB

Clinical Coordinating Center Personnel

Fernando Martinez, MD, MS

Co-Principal Investigator

Weill Cornell Medicine

1305 York Avenue

Box 96, Rm Y-1059

New York, NY 10021

T: 646-962-2748

E: fjm2003@med.cornell.edu

MeiLan Han, MD, MS

Co-Principal Investigator

University of Michigan

3916 Taubman Center

1500 E. Medical Center Dr.

Ann Arbor, MI 48109-5361

T: 734-936-5201

E: mrking@med.umich.edu

Barry Make, MD

National Jewish

1400 Jackson St., K729

Denver, CO 80206

T: 303-398-1993

E: makeb@njhealth.org

Barbara Yawn, MD, MSc

Chief Medical Officer

COPD Foundation

Washington, DC 20002

University of Minnesota

1963 112th Circle NE

Blaine, MN 55449

T: 507-261-3096

E: yawnx002@umn.edu

Randall Brown, MD, MPH

University of Michigan

2822 SPH I

1415 Washington Hts.

Ann Arbor, MI 48109-2029

T: 734-763-1549

E: rbrownmd@umich.edu

Anna Smyth, M.A.

Grants Administrator

Weill Cornell Medicine

1305 York Avenue, Y-1054

New York, NY 10021

T: 646-962-2743

E: ans2104@med.cornell.edu

Catherine Meldrum, PhD, RN, MS
Project Manager
University of Michigan
Taubman Center Floor 3 Reception C
1500 E. Medical Center Dr. SPC 5360
Ann Arbor, MI 48109
T: 734-647-7840
E: cathymel@umich.edu

Betsy Peters, BSN
Project Manager
Weill Cornell Medicine
1305 York Avenue, Y-1054
New York, NY 10021
T: 646-962-2742
E: elp2018@med.cornell.edu
<https://umich.app.box.com/folder/0>

11.1.7 12 MONTH SURVEY COORDINATING CENTER

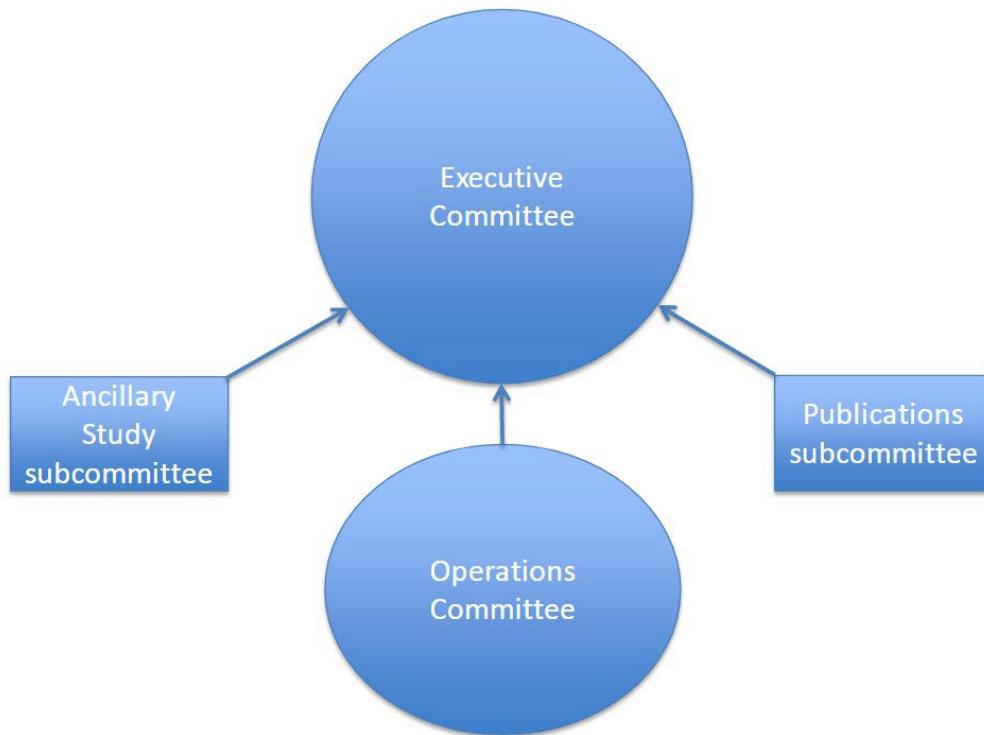
The 12 month Survey Coordinating Center will be led by Co-Investigator Barbara Yawn, MD MSc, Chief Science Officer at the COPD Foundation. Dr. Yawn will be responsible for oversight of the development and implementation of the reminder notices and 12 month survey administration by COPD Foundation study personnel for participants selected to complete the 12 month follow up survey.

11.2 ORGANIZATIONAL STRUCTURE

The Executive Committee will be led by the Principal Investigators and will consist of the 2 elected PBRN Directors, 1 representative of the COPD Foundation, Co-Investigators, Data Coordinating Center PI and Project Manager, NIH official and Clinical Coordinating Center Project Managers. The Executive Committee will meet every one-to-two weeks to administratively direct and monitor the progress of the study and to respond to any design, implementation or administrative issues that arise during the study.

The Operations Committee will consist of Overall Principal Investigators, PBRN Directors and lead coordinators, DCC Project Managers, and Co-Investigators. It will address implemental and administration faced by the PBRN practices that arise during the study.

Other subcommittees, such as the Publications and Ancillary Studies Subcommittees, will be constituted to support maximizing the utility of the CAPTURE study to the scientific community.



12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Comprehensive data coordinating center (DCC) functions for this clinical trial, including clinical monitoring, database development, web-based data entry and management, as well as the creation and export of study reports for the DSMB will be provided by the University of Michigan Statistical Analysis of Biomedical and Education Research (SABER) group. Housed in the top nationally ranked Department of Biostatistics, SABER, in its 17-year existence, has served as the DCC for over 50 studies, including multiple NIH-sponsored networks.

The DCC will use OpenClinica® (OpenClinica Clinical Trial Software; OpenClinica, LLC, Waltham, MA), a clinical trial software platform for electronic remote (i.e., site-based entry) data capture and clinical data management, as the basis for our custom-designed data entry and management system. The majority of data will be collected via electronic Case Report Forms (CRFs); however, other data sources, such as laboratory data from the central laboratory, may be used. In these circumstances, the DCC will also

utilize electronic data transfer. Protocols for the transfer of data, with careful attention to data integrity, will be written by experienced programmers and stored in the OpenClinica database or data mart.

The DCC has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous participant IDs on CRFs and in reports. OpenClinica® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

Data collection is the responsibility of the central study staff at the PBRN under the supervision of the PBRN Director (investigator). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Procedures which provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

13.2 STUDY RECORDS RETENTION

Study documents should be retained as required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting Drs. Martinez and Han.

14 PROTOCOL AMENDMENT HISTORY

| Protocol Amendment 2.0 - Summary of Changes | | | | |
|---|-------------|-----------------------|---|---|
| Location | Page Number | Type of Change | Description | Rationale |
| Cover Page | --- | <i>Administrative</i> | Update Protocol Version to 2.0 and update version date to | Amendment version and date |
| Cover Page | --- | <i>Administrative</i> | Add NCT # for each AIM | Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov |
| Table of Contents | --- | <i>Administrative</i> | Corrected page numbers for new version | Updating Table of Contents to reflect any page number shifts due to reformat |
| Multiple Sections | Multiple | <i>Administrative</i> | Changed Medical Chart Review to Medical Record Review throughout the protocol | Changed Medical Chart Review to Medical Record Review throughout the protocol |
| 1.2 Schema Table 1 | 9 | <i>Clarification</i> | Concomitant medications revised to read Respiratory Medications | Further clarification since these are limited to respiratory medication not all medications |

| | | | | |
|---|----|---------------|--|---|
| 1.2 Schema Table 1 | 9 | Clarification | Foot note 3 moved to 12 month to reflect the data that will be collected for subjects who qualify for 12 month follow-up w | Clarification that 12 month column is for indicating what data will be collected for subjects who meet 12 month follow-up criteria |
| 1.2 Schema Table 1 | 9 | Clarification | X in last column for 12 month spirometry was deleted. This was originally meant to be footnote that post bronchodilator spirometry would be performed at baseline for those subjects that qualified | Further clarification that spirometry will not be done at 12 month follow-up, the footnote was meant to reflect post bronchodilator spirometry at baseline for those subjects who qualify |
| Section 2.3.1 Known Potential Risks | 14 | Revision | For Albuterol: A targeted safety questionnaire will be administered to all participants prior to albuterol to exclude those with a previous adverse event with the medication and others at high risk due to cardiac abnormalities. | Subjects are excluded who have had MI and therefore not necessary |
| Section 4.1 Overall Study Design | 21 | Clarification | Patient-reported data will be collected by telephone, secure web-based server, and mail-based methodologies <u>based on participant preference and completed by the COPD Foundation</u> , as well as medical record abstraction, depending upon practice site preferences and feasibility. | The COPD Foundation will be collecting participant 12 month follow-up subject questionnaires |
| Section 4.1 Overall Study Design | 21 | Clarification | Clinic site data will also be collected from the Subject medical record data will be collected from the medical record to assess for changes in practice-level care. | Further clarification that this data will be collected from medical record |
| Section 6.3 Study Intervention Compliance | 27 | New | If results were not shared at the time of the CAPTURE study visit, then the date of sending the CAPTURE results will be recorded on the appropriate eCRF by filling in the date (day/month/year) the exact copy of the CAPTURE Tool results were sent to the clinician through a inter-clinic email or other HIPPA-compliant method and placed in the medical record. The goal is to communicate the results to the clinician in a timely manner within 3 business days. The DCC will monitor review all participants' eCRFs to assure that all those enrolled from practices randomized to CAPTURE results have been shared with clinicians in the specified timeframe. | The study team wanted to clarify that the exact copy of the CAPTURE tool should be shared with clinician. Also wanted to make timing of sharing less restrictive and the team recognized that restrictive parameters cannot always be realized in clinical practice setting |

| | | | | |
|---|-----------|-----------------------|--|--|
| Section 8.2 Longitudinal Follow-up Assessment and Data Collection | 30 | <i>Clarification</i> | Medical chart abstractions <u>completed by PBRN coordinators</u> and participant questionnaires <u>administered by study team</u> <u>members from the COPD</u> <u>Foundation are used.</u> | Clarification that medical chart reviews will be done by PBRN coordinators and COPD Foundation will administer participant questionnaires at 12 months |
| Section 8.2 Longitudinal Follow-up Assessment and Data Collection | 30 | <i>Clarification</i> | Data from clinical visits to be collected at follow-up by telephone, secure web-based server, or mail-based methodologies directly from participants <u>and administered by</u> <u>COPD Foundation study personnel</u> | Clarification that COPD Foundation will administer participant questionnaires at 12 months |
| Section 10.1.1 Informed Consent Process | 45 | <i>New</i> | All PBRN research coordinators, <u>COPD Foundation study staff</u> and other clinical investigators will be certified by their local IRB in informed consent and human studies research. | The COPD Foundation has attained IRB approval as their team will be interacting with participants |
| Section 10.1.3 Confidentiality and Privacy | 46 | <i>Clarification</i> | In addition, it may be transmitted and stored at the DCC in a database separate from the clinical database (used for statistical analysis and scientific reporting) and with <u>COPD Foundation study</u> <u>team</u> study coordinator access to aid in contacting participants at the 12-month follow-up. | COPD Foundation will have access to participant contact information from a separate database in order to contact participants for follow-up questionnaire completion |
| Section 11.1.2 Practice Based Research Networks (PBRN) | 47 | <i>Administrative</i> | Moved Roles and Responsibilities to section 11.1.2 | Moved Roles and Responsibilities to section 11.1.2 |
| Section 11.1.2 Practice Based Research Networks (PBRN) | 47 | <i>Revision</i> | Change Carolinas HealthCare System to Atrium Health and add new PI for Oregon Rural Practice-Based Research Network | Carolinas HealthCare System is now Atrium Health and the new PI at Oregon, Dr. Lyle Fagnan is retiring and Dr. Nancy Elder will take his place as director and site PI for CAPTURE |
| Section 11.1.7 Clinical Coordinating Center | 49 | <i>Clarification</i> | Update titles for COPD Foundation study members | Administrative change to include titles for Dr. Yawn |
| Section 11.1.8 12 Month Survey Coordinating Center | 50 | <i>New</i> | Add 12 Month Survey Coordinating Center to Study Leadership, Section 11. | The COPD Foundation study team will be coordinating outreach to 12 month follow-up subjects and administering surveys |
| Section 11.2 Organizational Structure | 51 | <i>Clarification</i> | Includes 1 representative of the COPD Foundation in the Executive Committee Organization description. | COPD Foundation representatives are part of the Executive Committee currently |
| Section 4.1 Overall Study Design | 9, 10, 21 | <i>New</i> | Deletion of CAT Score \geq 10 and CAPTURE Score \geq 2 and return to CAPTURE+ and abnormal spirometry as longitudinal follow-up criteria | The study team proposes to defer longitudinal follow-up based solely on an isolated, baseline CAT or CAPTURE scores as it is outside the scope of the current CAPTURE program. The study team is also proposing to return to the original scientific approach to follow CAPTURE+ (as defined in the protocol) subjects along with abnormal post-BD spirometry and 5% |

| | | | | |
|--|-----------|-----|---|---|
| | | | | random sample of those subjects that meet neither of these criteria. Those subjects already selected under the current algorithm would still be followed longitudinally (and noted as selected under the initial follow-up selection criteria) and would use data as appropriate. Importantly, the primary care clinician colleagues within the CAPTURE program do not feel there is a safety issue in not following this population as there are no data defining a negative impact of an isolated, elevated CAT score in primary care patients. |
| Section 1.1 Synopsis, Section 4.1 Overall Study Design, Section 8.1 Baseline Assessments and Data Collection | 3, 20, 29 | New | Addition of adjudication of the presence of obstruction on post-bronchodilator spirometry | As the study commenced, several instances of the faulty spirometry software reading incomplete or participant refusal of post-bronchodilator occurred and led to the need for spirometry core to determine review process in these instances and validity of pre-bronchodilator spirometry. The rationale for this is that in other databases where all patients had both pre and post-bronchodilator spirometry, those who had a pre-bronchodilator FEV1/FVC less than 0.65 had a post-bronchodilator FEV1/FVC less than 0.70 more than 95% of the time. |
| 8.1 Baseline Assessments and Data Collection | 28 | New | Addition of spirometry instructions if participant has taken a medicine they breathed into lungs from puffer or inhaler within two hours of spirometry test | Since study start, one participant reported taking albuterol shortly before the visit. The study clinicians confirmed this scenario would constitute the participant being in a post-bronchodilator state already with no further need to proceed after initial spirometry. The data collection process has been updated to assure these values would be placed in post-bronchodilator data. Coordinators are instructed to ask this question before spirometry should this scenario occur again during the study. |

Protocol Amendment 3.0 - Summary of Changes

| Location | Page Number | Type of Change | Description | Rationale |
|----------------------|-------------|----------------|---|---|
| Cover Page | --- | Administrative | Update Protocol Version to 3.0 and update version date to 24 September 2019 | Amendment version and date updated |
| Cover Page | --- | Administrative | Add NCT # for each AIM | Add all 3 numbers to protocol since each AIM is registered in clinicaltrials.gov |
| Multiple Sections | Multiple | Revision | Number of PBRNs participating in aims 1 and 2 revised to 6 PBRNs throughout protocol. | Additional PBRN added |
| 1.2 Schema Table 1 | 9 | Revision | CAPTURE 12 additional items questionnaire | The CAPTURE 12 item additional questionnaire was renamed. |
| Section 8.1 Baseline | 30 | Clarification | CAPTURE Additional Items Questionnaire administration | Further instruction for administration of CAPTURE Additional Items Questionnaire, |

| Assessments and Data Collection | | | instruction added to Study Assessments. | as described in Section 1.2 Schema table, was added. |
|--|-------------|----------------|--|--|
| Section 11.1.2 Practice Based Research Networks (PBRN) | 48 | Revision | University of Illinois, Chicago added as a participating PBRN. | University of Illinois, Chicago added as an enrolling site in aims 1 and 3. |
| Protocol Amendment 4.0 - Summary of Changes | | | | |
| Location | Page Number | Type of Change | Description | Rationale |
| Protocol Amendment Summary of Changes Table | --- | Administrative | Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table. | Amendment 2.0 – Summary of Changes was added to provide a comprehensive list of changes across all protocol amendments. |
| Protocol Amendment 5.0 - Summary of Changes | | | | |
| Location | Page Number | Type of Change | Description | Rationale |
| 1.2 Schema Table 1, 8.2 Longitudinal follow-up assessment | 9, 32 | New | A COVID-19 questionnaire was added to the 12-month follow-up visit, performed by the COPD Foundation. | A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes. |
| 2.1 Study Rationale, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design | 11, 22, 23 | New | Rationale for collecting COVID-19 information from participants was added. | The impact of COVID-19 on COPD Case Finding and respiratory symptoms in primary care is unknown. COVID-19 information will be used to investigate this. |
| 4.1 Overall Study Design | 21 | Revision | The following change was made: Participants who meet the criteria for follow-up will be sent notification/reminder letters <u>within the first 3 weeks of shortly after enrollment and receive</u> at 3, 6, and 9 months | Language was updated for flexibility in notification of participants in order to allow time to confirm follow-up criteria. |
| 8.1 Baseline Assessments and Data Collection | 29 | Revision | Additional guidance for sites to follow their local institutional guidelines for spirometry was added. | Institutional guidance for minimizing the risk of COVID-19 spread during spirometry varies across sites. Sites should ensure they are following local guidance. |
| 8.3 Aim 2 Assessments | 34 | Revision | Participants will receive a \$15 gift card for completion of the opinion survey, instead of \$10. | This was a typo in the prior version of the protocol. |
| 8.2 Longitudinal follow-up assessment | 31 | New | Extraction of data related to COVID-19 confirmed and suspected cases will be added to the 12 month medical record review. | A COVID-19 questionnaire was added to collect information about the COVID-19 prevalence in primary care, impact on symptoms, relation to comorbidities, and impact on provider outcomes. |
| Protocol Amendment Summary of Changes Table | --- | Administrative | Protocol Amendment 2.0 – Summary of Changes was added to the Summary of Protocol Amendments Table. | Summary of Changes for protocol versions 2.0 and 3.0 –were added to Section 14 to provide a comprehensive list of changes across all protocol amendments. |
| Protocol Amendment 6.0 - Summary of Changes | | | | |
| Location | Page Number | Type of Change | Description | Rationale |

| Cover page | --- | Administrative | Update Protocol Version to 6.0 and update version date to 10 JAN 2022 | Amendment version and date |
|---|-----|----------------|---|---|
| 1.1 Synopsis Definitions | 3 | Revision | Language related to normal PEF has been changed to greater than or equal to the measurement ranges for males and females. "...defined as ≥ 350 L/min for males and ≥ 250 L/min for females" | The previous sentence stated that the PEF scores needed to be greater to 350 L/min or 250 L/min and not inclusive of these values. |
| 1.1 Synopsis Definitions | 3 | Revision | Language related to exacerbations been changed to greater than or equal 1. " ≥ 1 exacerbation-like event within the past 12 months." | The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations. |
| 1.1 Study Population | 6 | Revision | The overall N has been changed to approximately 5000. (total N = ≤ 5000) | The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document. |
| 2.1 Study Rationale | 11 | Revision | We will conduct a 5,000 participant cohort study of <u>approximately 5,000 participants</u> | The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document. |
| 2.2 Background | 13 | Revision | Language related to exacerbations been changed to greater than or equal 1. "...COPD with ≥ 1 ECOPD" | The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations. |
| 4.1 Overall Design | 20 | Revision | Language related to normal PEF has been changed to greater than or equal to the measurement ranges for females. " ≥ 250 L/min for females" | The previous sentence stated that the PEF scores needed to be greater to 350 L/min or 250 L/min and not inclusive of these values. Participants with PEF values greater than or equal to 350 L/min (males) or 250 L/min (females) are CAPTURE Negative. |
| 4.1 Overall Design | 20 | Revision | Language related to exacerbations been changed to greater than or equal 1. "... ≥ 1 exacerbation like event within the past 12 months." | The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations. |
| 9.1.1.1 Sensitivity and Specificity of the CAPTURE Tool | 39 | Revision | Language related to exacerbations been changed to greater than or equal 1. "... either >1 exacerbation-like event (ECOPD) within the past 12 months" | The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations. |
| 9.1.1.3 Sensitivity and Specificity of the CAPTURE Tool | 41 | Revision | "(for a total of <u>approximately</u> 5,000-patients)." The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document. | The DSMB approved the reduction of enrollment from 5000 but the study will aim to enroll as many participants as possible. This has been reflected throughout the document. |

| 9.2 Population for Analyses | 42 | Revision | Language related to exacerbations been changed to greater than or equal 1. “...>1 exacerbation-like event (ECOPD)” | The previous sentence stated that the number of exacerbations need to be greater than 1 but was not inclusive of 1. The new statement is to clarify that clinically significant COPD includes 1 or more exacerbations. |
|--|----------------|----------------|---|---|
| Protocol Amendment 7.0 - Summary of Changes | | | | |
| Location | Page Number | Type of Change | Description | Rationale |
| Cover page | --- | Administrative | Update Protocol Version to 7.0 and update version date to 25JUN2023 | Amendment version and date |
| Abbreviations | 2 | Administrative | PRISm- Preserved ratio, impaired spirometry SNO- Symptomatic non-obstructed | 2 new abbreviations have been added to this table. |
| 1.1 Synopsis | 3 | Addition | Definitions: <u>Preserved ratio, impaired spirometry</u> (PRISm) = Participants without spirometrically defined COPD who have post-bronchodilator FEV1 < 80% predicted. • <u>Symptomatic non-obstructed (SNO)</u> = Participants without spirometrically defined COPD and without PRISm who have a COPD Assessment Test score ≥ 10. | 2 new Definitions have been added to define the following terms: PRISm- Preser4ved ratio, impaired spirometry SNO- Symptomatic non-obstructed |
| 1.1 Synopsis | 4 | Edit | Objectives: • Aim 3 – Define the impact of CAPTURE information provided to clinicians in identifying and managing CAPTURE+ patients with respiratory symptoms (CAPTURE+) across a broad range of primary care settings. | Under Objectives, Aim3 has been edited to properly describe CAPTURE+ patients |
| 1.1 Synopsis | 5 | Clarification | Objectives: • Aim 3 - • Define the impact of <u>providing</u> CAPTURE-clinician-education, and patient- level CAPTURE information to clinicians (“ <u>CAPTURE education</u> ”) on selected <u>clinician additional</u> therapeutic interventions in previously undiagnosed patients with clinically significant COPD <u>for the management</u> of CAPTURE+ patients. • Assess <u>the impact of CAPTURE</u> <u>education and patient-level CAPTURE</u> <u>information on clinician interventions</u> specific to smokers <u>who are</u> CAPTURE+. • <u>Determine the impact of CAPTURE</u> <u>education and patient-level CAPTURE</u> <u>information on patient symptoms,</u> <u>exacerbations, hospitalizations, and</u> | This amendment clarifies Aim 3 and the analyses that are being conducted. |

| | | | | |
|--------------|-----|---------------|---|--|
| | | | <p><u>mortality among CAPTURE+ patients.</u></p> <ul style="list-style-type: none"> • <u>Determine the impact of CAPTURE education on patient symptoms, exacerbations, hospitalizations, and mortality.</u> • <u>Determine the impact of CAPTURE education and receipt of patient-level CAPTURE information on when COPD is defined spirometrically identification and management of patients with respiratory burden.</u> | |
| 1.1 Synopsis | 6 | Addition | <p>Endpoints:</p> <ul style="list-style-type: none"> • Aim 3 – <p>O Proportion of CAPTURE+ participants who meet at least one of the following within 12 months of study baseline (composite endpoint): 1) referral for or completion of clinical spirometry testing, 2) new diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/treatment, or 5) <u>referral for or completion of pulmonary rehabilitation.</u></p> | <p>Aim 3 Endpoints now includes the analysis of referral or completion of pulmonary rehab at the 12 month follow up.</p> |
| 1.1 Synopsis | 6,7 | Clarification | <p>Secondary Endpoints</p> <ul style="list-style-type: none"> • Aim 3 – <p><u>Proportion of CAPTURE+ participants who have each of the following occur within 12 months of study baseline (separate endpoints to be evaluated individually): 1-5) each component of the Aim 3 primary endpoint, and 6) recommendation or administration of influenza vaccination- patients who meet the components of the composite endpoint.</u></p> <p>O <u>Proportion of patients with clinically significant COPD who meet the composite endpoint.</u></p> <p>O <u>Proportion of CAPTURE+ participants currently smoking at the baseline study visit who have any of the components of the Aim 3 primary endpoint or any of the following occur within 12 months of baseline (evaluated as a composite endpoint and as individual endpoints): 1) clinician counseling or recommendation for smoking cessation, 2) referral to a smoking cessation program, 3) referral to a smoking quit line, and 4) newly prescribed medication for smoking cessation. In participants with clinically significant COPD who are current smokers, the incidence of physician-referral to a formal smoking cessation program, prescribed smoking cessation medication, and referral to pulmonary</u></p> | <p>Clarification of the secondary endpoints and what participants will be analyzed.</p> |

| | | | | |
|------------------------------|----|----------|--|--|
| | | | <p>rehabilitation program.</p> <p>O In CAPTURE+ participants, change in CAT score between baseline and follow-up at 12 months after baseline, and proportion of patients who experience exacerbations, hospitalizations, or mortality within 12 months of baseline. In participants with clinically significant COPD, change in CAT score, and proportion of patients who experience exacerbations, hospitalizations, or mortality.</p> <p>O All of the above endpoints for Aim 3, in the population of participants defined by each of the following instead of CAPTURE+ status: 1) clinically significant COPD, 2) spirometric COPD, 3) preserved ratio, impaired spirometry (PRISm), and 5) symptomatic non-obstructed (SNO). All of the above endpoints for Aim 3, with the patient population defined as those who have COPD defined spirometrically.</p> <p>O All of the above endpoints for Aim 3, in all of the analysis populations named above, separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic.</p> | |
| 1.3 Schedule of Assessments | 11 | Edit | <p>Footnote 3:</p> <p>3. Recorded for a subset of participants who meet any of the following criteria:</p> <p>1) CAPTURE+ subjects defined as CAPTURE Score > 5 or CAPTURE score of 2, 3, or 4 with a low PEF, defined as <350 L/min for males and <250 L/min for females 2) abnormal spirometry defined as post-bronchodilator FEV1/FVC < 0.70 or FEV1 < 80% predicted at baseline, or pre-bronchodilator FEV1/FVC < 0.65 or FEV1 < 70% predicted for patients who do not complete post-bronchodilator spirometry;</p> | <p>The footnote was edited to include more information regarding the spirometry testing and what is defined as abnormal.</p> |
| 3.0 Objectives and Endpoints | 18 | Edit | <p>Aim 3 Objectives and Endpoints have been updated to reflect changes throughout the study. Aim 3 changes for Objectives, Endpoints, and Justifications have been made in this table</p> | <p>The Aim 3 clarifications noted above, are reflected in the edits of this table.</p> |
| 4.1 Overall Design | 24 | Addition | <p>PRISm and SNO have been added to the Cohort Table.</p> <p>PRISm- Participants without spirometrically defined COPD who have post-bronchodilator FEV1 < 80%</p> | <p>PRISm and SNO Cohorts have been added to reflect the changes in the protocol.</p> |

| | | | | |
|--|----|---------------|--|--|
| | | | <p><u>predicted.</u></p> <p><u>SNO- Participants without spirometrically defined COPD and without PRISM who have a COPD Assessment Test score ≥ 10.</u></p> | |
| 4.1 Overall Design | 24 | Clarification | <p>Longitudinal Follow Up</p> <p>2. Participants who have abnormal spirometry results, defined as post-bronchodilator FEV1/FVC < 0.7 or FEV1 < 80% predicted at baseline. If a participant is unable to complete a post- bronchodilator spirometry (refusal, technical error on the part of coordinator, etc.), and the pre- bronchodilator FEV1/FVC is less than 0.65 <u>or FEV1 is less than 70% predicted</u>, the participant will be considered to have <u>COPD abnormal spirometry</u> for the purpose of follow-up in this study.</p> | This clarifies what constitutes as an Abnormal Spirometry in CAPTURE which would lead to a follow up 12 months after the initial visit. |
| 8.2 Longitudinal Follow-Up Assessments and Data Collection | 34 | Addition | <p>Medical Record Data Collection</p> <p>Current Smokers Only:</p> <p><u>New prescription for smoking cessation medication</u></p> <p><u>Referral to a smoking quit line</u></p> | Medical record review will now collect data about new prescriptions for smoking cessation medication and referrals to a smoking quit line for current smokers. |
| 8.2 Longitudinal Follow-Up Assessments and Data Collection | 35 | Addition | <p>Data Collection by the COPD Foundation</p> <p>Current Smokers Only:</p> <p><u>Smoking cessation counseling Referral to a smoking cessation program</u></p> <p><u>Smoking cessation medications (including OTC) Referral to a smoking quit line</u></p> <p>New prescription for smoking cessation medication</p> <p><u>Over-the-counter patches/gum for smoking cessation</u></p> <p>All participants undergoing 12-month follow-up as described in section 4.1:</p> <p><u>Spirometry referral/completion</u></p> <p><u>Deleted * and footnote for *</u></p> | Data collected by the COPD Foundation will now include information referrals to a smoking cessation program and a smoking quit line as well as medications, including over the counter medications, for current smokers. |
| 9.1.1.3 Practice Behavior in Sites With Versus Without Capture Education and Patient Level | 43 | Clarification | From <u>medical record review and follow-up patient survey responses</u> , the composite endpoint is met if one of the following is recorded: (1) <u>referral for or completion of clinical spirometry testing</u> , 2) new clinical | Clarification about what is collected during the medical record review for hypothesis 3 has been included in this paragraph. The addition of referral or completion of pulmonary rehab was also included for analysis. |

| | | | | |
|---------------------------------|----|---------------|---|--|
| Capture Data Provided | | | diagnosis of COPD, 3) newly prescribed respiratory medication (long acting bronchodilator or anti-inflammatory for respiratory condition), or 4) referral to a specialist for respiratory evaluation/ treatment, <u>or 5) referral for or completion of pulmonary rehabilitation.</u> | |
| 9.2 Populations for Analyses | | Clarification | Aim 3: Populations used in 2-sample comparisons of the average proportion of CAPTURE+ patients per practice that meet the composite endpoint in outcomes between the two intervention arms will be based on randomization group (intent-to-treat analysis). | This change clarifies how the samples will be analyzed for Aim 3. |
| 9.2 Populations for Analyses | 45 | Addition | Aim 3: <u>For primary analysis of each Aim 3 outcome, the analysis population will consist of all patients with follow-up data for that outcome from both the medical record review and the patient survey administered by the COPD Foundation (section 8.2).</u> <u>Secondary analyses will be performed using alternative analysis populations, including</u> <u>1. All patients with outcome data from the medical record review, and</u> <u>2. All patients selected for follow-up.</u> | Additional information regarding the primary analysis of Aim 3 outcomes is now included in this section. |
| 9.3.2 Practice Behavior (Aim 3) | 46 | Clarification | Additional language regarding how the Aim 3 primary endpoint and analysis is included in this section. | |
| 9.3.2 Practice Behavior (Aim 3) | 46 | Edit | <u>5) an identity link function so that the coefficient parameter corresponding to CAPTURE intervention group represents a difference in outcome probability a logistic link function</u> | This was edited to provide more information about the link function analysis. |
| 9.3.2 Practice Behavior (Aim 3) | 46 | Addition | <u>For each Aim 3 outcome that is collected via both medical record review and patient survey, the primary analysis will be among patients with complete outcome data from both the medical record and patient survey.</u> <u>Sensitivity analyses will be conducted by imputing missing outcome data using different assumptions and applying the primary analysis method to the resulting data sets.</u> <u>Sensitivity analyses will include (1) imputation of negative responses (i.e., responses indicating that the outcome has not occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review</u> | This paragraph was added to provide additional information surrounding the analyses of Aim 3. |

| | | | | |
|---------------------------------|----|---------------|--|--|
| | | | <p><u>data; (2) imputation of positive responses (i.e., responses indicating that the outcome has occurred) for all missing patient survey responses, followed by analysis of all patients with medical record review data; and (3) multiple imputation of all missing outcome data using the observed outcomes and covariates, followed by analysis of all patients selected for follow-up.</u></p> | |
| 9.3.2 Practice Behavior (Aim 3) | 47 | Clarification | <p><u>Subject to having sufficient mortality events, survival</u></p> | This statement clarifies that how the survival analysis and mortality events will be analyzed. |
| 9.3.2 Practice Behavior (Aim 3) | 47 | Addition | <p>All additional secondary analyses will also be applied to patients with clinically significant and spirometrically defined COPD, PRISM, and symptomatic non-obstruction.</p> | Secondary analyses include PRISM and SNO as reflected throughout the protocol. |
| 9.3.2 Practice Behavior (Aim 3) | 47 | Clarification | <p>Practices that do not have any <u>clinically significant COPD or spirometrically defined COPD patients with these conditions</u></p> | Practices that do not have conditions defined in the cohorts will not be used in secondary analyses. |
| 9.3.2 Practice Behavior (Aim 3) | 47 | Addition | <p><u>Analyses will be repeated in populations separated into cohorts based on enrollment date and the degree to which follow-up may have been affected by the SARS-CoV-2 pandemic.</u></p> | There may be additional analyses due to SARS-CoV-2 and its effects on follow up data. |

15 LITERATURE REFERENCES

1. Martinez FJ, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP, High-Risk CSSG. A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2017;195(6):748-56. doi: 10.1164/rccm.201603-0622OC. PubMed PMID: 27783539; PMCID: PMC5363964.
2. Brown DW, Croft JB, Greenlund KJ, Giles WH. Trends in hospitalization with chronic obstructive pulmonary disease—United States, 1990–2005. *Copd.* 2010;7(1):59-62. doi: 10.3109/15412550903499548. PubMed PMID: 20214464.
3. Centers for Disease Control and Prevention. Deaths from chronic obstructive pulmonary disease – United States 2000–2005. *Morbidity and Mortality Weekly Report.* 2008;57(45):1229-32.
4. Kochanek KD, Xu J, Murphy SL, Minino AM, Kung HC. Deaths: final data for 2009. *Natl Vital Stat Rep.* 2011;60(3):1-117.
5. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(9995):743-800. doi: 10.1016/S0140-6736(15)60692-4. PubMed PMID: 26063472; PMCID: PMC4561509.
6. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, Yusuf S. The burden of disease in older people and implications for health policy and practice. *Lancet.* 2015;385(9967):549-62. doi: 10.1016/S0140-6736(14)61347-7. PubMed PMID: 25468153.
7. Martinez CH, Mannino DM, Jaimes FA, Curtis JL, Han MK, Hansel NN, Diaz AA. Undiagnosed Obstructive Lung Disease in the United States. Associated Factors and Long-term Mortality. *Ann Am Thorac Soc.* 2015;12(12):1788-95. doi: 10.1513/AnnalsATS.201506-388OC. PubMed PMID: 26524488; PMCID: PMC4722830.
8. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration; international review of thoracic diseases.* 2005;72(5):471-9. doi: 10.1159/000087670. PubMed PMID: 16210885.
9. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatius L, Burney P, Miravitles M, Garcia-Rio F, Akbari K, Ancochea J, Menezes AM, Perez-Padilla R, Montes de Oca M, Torres-Duque CA, Caballero A, Gonzalez-Garcia M, Buist S, Bold Collaborative Research Group tEPISTtPT, the PSG, Team BCRGtE-STtP, the PSG. Determinants of underdiagnosis of COPD in national and international surveys. *Chest.* 2015;148(4):971-85. doi: 10.1378/chest.14-2535. PubMed PMID: 25950276.
10. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, Heels-Ansdel DM, Erak M, Bragaglia PJ, Tamari IE, Hodder R, Stanbrook MB. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ.* 2010;182(7):673-8. doi: 10.1503/cmaj.091784. PubMed PMID: 20371646; PMCID: PMC2855915.
11. Labonte LE, Tan WC, Li PZ, Mancino P, Aaron SD, Benedetti A, Chapman KR, Cowie R, FitzGerald JM, Hernandez P, Maltais F, Marciniuk DD, O'Donnell D, Sin D, Bourbeau J, Canadian Respiratory

Research N, Can CCRG. Undiagnosed Chronic Obstructive Pulmonary Disease Contributes to the Burden of Health Care Use. Data from the CanCOLD Study. *Am J Respir Crit Care Med.* 2016;194(3):285-98. doi: 10.1164/rccm.201509-1795OC. PubMed PMID: 26836958.

12. Guiguis-Blake J, Senger C, Webber E, Mularski R, Whitlock E. Screening for Chronic Obstructive Pulmonary Disease: A Systematic Evidence Review for the U.S. Preventive Services Task Force. *Evidence Synthesis No. 130.* Publication No. 14-0525-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

13. Martinez FJ, O'Connor GT. Screening, Case-Finding, and Outcomes for Adults With Unrecognized COPD. *JAMA.* 2016;315(13):1343-4. doi: 10.1001/jama.2016.3274. PubMed PMID: 27046363.

14. Joo MJ, Sharp LK, Au DH, Lee TA, Fitzgibbon ML. Use of spirometry in the diagnosis of COPD: a qualitative study in primary care. *Copd.* 2013;10(4):444-9. doi: 10.3109/15412555.2013.766683. PubMed PMID: 23537230; PMCID: PMC3938329.

15. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. *Chest.* 2000;117(4):1146-61. doi: 10.1378/chest.117.4.1146 PubMed PMID: 10767253.

16. Han MK, Kim MG, Mardon R, Renner P, Sullivan S, Diente GB, Martinez FJ. Spirometry utilization for COPD: how do we measure up? *Chest.* 2007;132(2):403-9. doi: 10.1378/chest.06-2846. PubMed PMID: 17550936.

17. Joo MJ, Lee TA, Weiss KB. Geographic variation of spirometry use in newly diagnosed COPD. *Chest.* 2008;134(1):38-45. doi: 10.1378/chest.08-0013. PubMed PMID: 18347201.

18. Volkova NB, Kodani A, Hilario D, Munyaradzi SM, Peterson MW. Spirometry utilization after hospitalization for patients with chronic obstructive pulmonary disease exacerbations. *Am J Med Qual.* 2009;24(1):61-6. doi: 10.1177/1062860608326417. PubMed PMID: 19139465.

19. Nishi SP, Wang Y, Kuo YF, Goodwin JS, Sharma G. Spirometry use among older adults with chronic obstructive pulmonary disease: 1999-2008. *Ann Am Thorac Soc.* 2013;10(6):565-73. doi: 10.1513/AnnalsATS.201302-037OC. PubMed PMID: 24053440; PMCID: PMC3960963.

20. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E, Bold Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet.* 2007;370(9589):741-50. doi: 10.1016/S0140-6736(07)61377-4. PubMed PMID: 17765523.

21. Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Price D, Halbert RJ. Questions for COPD diagnostic screening in a primary care setting. *Respiratory medicine.* 2005;99(10):1311-8. doi: 10.1016/j.rmed.2005.02.037. PubMed PMID: 16140231.

22. Enright PL. Should we keep pushing for a spirometer in every doctor's office? *Respir Care.* 2012;57(1):146-51;discussion 51-3. doi: 10.4187/respcare.01504. PubMed PMID: 22222133.

23. Murphy DE, Panos RJ. Diagnosis of COPD and clinical course in patients with unrecognized airflow limitation. *International journal of chronic obstructive pulmonary disease.* 2013;8:199-208. doi: 10.2147/COPD.S39555. PubMed PMID: 23637527; PMCID: PMC3634319.

24. Miravitles M, Soriano J, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax*. 2009;64:863-8.
25. Mapel DW, Robinson SB, Dastani HB, Shah H, Phillips AL, Lydick E. The direct medical costs of undiagnosed chronic obstructive pulmonary disease. *Value Health*. 2008;11(4):628-36. doi: 10.1111/j.1524-4733.2007.00305.x. PubMed PMID: 18194402.
26. Akazawa M, Halpern R, Riedel AA, Stanford RH, Dalal A, Blanchette CM. Economic burden prior to COPD diagnosis: a matched case-control study in the United States. *Respiratory medicine*. 2008;102(12):1744-52. doi: 10.1016/j.rmed.2008.07.009. PubMed PMID: 18760581.
27. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Annals of internal medicine*. 2007;147(9):633-8. PubMed PMID: 17975186.
28. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK. Executive summary: prevention of acute exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147(4):883-93. doi: 10.1378/chest.14-1677. PubMed PMID: 25320966; PMCID: PMC4388123.
29. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. *Lancet*. 2015;385(9979):1778-88. doi: 10.1016/S0140-6736(15)60647-X. PubMed PMID: 25943942; PMCID: 4819246.
30. Decramer M, Miravitles M, Price D, Roman-Rodriguez M, Llor C, Welte T, Buhl R, Dusser D, Samara K, Siafakas N. New horizons in early stage COPD--improving knowledge, detection and treatment. *Respiratory medicine*. 2011;105(11):1576-87. doi: 10.1016/j.rmed.2010.12.015. PubMed PMID: 21239156.
31. Calverley PM, Nordyke RJ, Halbert RJ, Isonaka S, Nonikov D. Development of a population-based screening questionnaire for COPD. *Copd*. 2005;2(2):225-32. PubMed PMID: 17136949.
32. van Schayck CP, Halbert RJ, Nordyke RJ, Isonaka S, Maroni J, Nonikov D. Comparison of existing symptom-based questionnaires for identifying COPD in the general practice setting. *Respirology*. 2005;10(3):323-33. doi: 10.1111/j.1440-1843.2005.00720.x. PubMed PMID: 15955145.
33. Yawn BP, Mapel DW, Mannino DM, Martinez FJ, Donohue JF, Hanania NA, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Dalal AA, Lung Function Questionnaire Working Group. Development of the Lung Function Questionnaire (LFQ) to identify airflow obstruction. *International journal of chronic obstructive pulmonary disease*. 2010;5:1-10. doi: 10.2147/COPD.S7683. PubMed PMID: 20368906; PMCID: 2846155.
34. Martinez FJ, Raczek AE, Seifer FD, Conoscenti CS, Curtice TG, D'Eletto T, Cote C, Hawkins C, Phillips AL, Group C-PCW. Development and initial validation of a self-scored COPD Population Screener Questionnaire (COPD-PS). *Copd*. 2008;5(2):85-95. doi: 10.1080/15412550801940721. PubMed PMID: 18415807; PMCID: 2430173.

35. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, Juniper EF, Freeman D, Hausen T, Levy ML, Ostrem A, van der Molen T, van Schayck CP. Symptom-based questionnaire for identifying COPD in smokers. *Respiration; international review of thoracic diseases*. 2006;73(3):285-95. doi: 10.1159/000090142. PubMed PMID: 16330875.
36. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. *Chest*. 2006;129(6):1531-9. doi: 10.1378/chest.129.6.1531. PubMed PMID: 16778271.
37. Raghavan N, Lam YM, Webb KA, Guenette JA, Amornputtisathaporn N, Raghavan R, Tan WC, Bourbeau J, O'Donnell DE. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. *Copd*. 2012;9(2):175-83. doi: 10.3109/15412555.2011.650802. PubMed PMID: 22409441.
38. Kotz D, Nelemans P, van Schayck CP, Wesseling GJ. External validation of a COPD diagnostic questionnaire. *The European respiratory journal*. 2008;31(2):298-303. doi: 10.1183/09031936.00074307. PubMed PMID: 17959636.
39. Haroon S, Jordan R, Takwoingi Y, Adab P. Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. *BMJ Open*. 2015;5(10):e008133. doi: 10.1136/bmjopen-2015-008133. PubMed PMID: 26450427; PMCID: PMC4606431.
40. Haroon S, Jordan RE, Fitzmaurice DA, Adab P. Case finding for COPD in primary care: a qualitative study of the views of health professionals. *International journal of chronic obstructive pulmonary disease*. 2015;10:1711-8. doi: 10.2147/COPD.S84247. PubMed PMID: 26357469; PMCID: PMC4559237.
41. Nelson SB, LaVange LM, Nie Y, Walsh JW, Enright PL, Martinez FJ, Mannino DM, Thomashow BM. Questionnaires and pocket spirometers provide an alternative approach for COPD screening in the general population. *Chest*. 2012;142(2):358-66. doi: 10.1378/chest.11-1474. PubMed PMID: 22194590.
42. Leidy NK, Malley KG, Steenrod AW, Mannino DM, Make BJ, Bowler RP, Thomashow BM, Barr RG, Rennard SI, Houfek JF, Yawn BP, Han MK, Meldrum CA, Bacci ED, Walsh JW, Martinez F. Insight into Best Variables for COPD Case Identification: A Random Forests Analysis. *Chronic Obstr Pulm Dis (Miami)*. 2016;3(1):406-18. doi: 10.15326/jcopdf.3.1.2015.0144. PubMed PMID: 26835508; PMCID: PMC4729451.
43. Leidy NK, Kim K, Bacci ED, Yawn BP, Mannino DM, Thomashow BM, Barr RG, Rennard SI, Houfek JF, Han MK, Meldrum CA, Make BJ, Bowler RP, Steenrod AW, Murray LT, Walsh JW, Martinez F, High-Risk CSSG. Identifying cases of undiagnosed, clinically significant COPD in primary care: qualitative insight from patients in the target population. *NPJ Prim Care Respir Med*. 2015;25:15024. doi: 10.1038/npjpcrm.2015.24. PubMed PMID: 26028486; PMCID: PMC4532157.
44. Eremenco SL, Celli D, Arnold BJ. A comprehensive method for the translation and cross-cultural validation of health status questionnaires. *Eval Health Prof*. 2005;28(2):212-32. doi: 10.1177/0163278705275342. PubMed PMID: 15851774.
45. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, Lopez Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agusti A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. *GOLD Executive*

Summary. Am J Respir Crit Care Med. 2017;195(5):557-82. doi: 10.1164/rccm.201701-0218PP. PubMed PMID: 28128970.

46. Johnson K, Tuzzio L, Renz A, Baldwin LM, Parchman M. Decision-to-Implement Worksheet for Evidence-based Interventions: From the WWAMI Region Practice and Research Network. J Am Board Fam Med. 2016;29(5):553-62. doi: 10.3122/jabfm.2016.05.150327. PubMed PMID: 27613788; PMCID: PMC5065058.
47. Practice Facilitation Handbook: Module 5. Mapping and Redesigning Workflow.: Agency for Healthcare Research and Quality Website.; Updated May 2013 [cited 2018 January 23]. Available from: <https://www.ahrq.gov/professionals/prevention-chronic-care/improve/system/pfhandbook/mod5.html>.
48. Onwuegbuzie A, Dickinson W, Leech N, Zoran A. A qualitative framework for collecting and analyzing data in focus group research. Int J Qual Meth. 2009;8(3):1-21.
49. Wong SS, Abdullah N, Abdullah A, Liew SM, Ching SM, Khoo EM, Jiwa M, Chia YC. Unmet needs of patients with chronic obstructive pulmonary disease (COPD): a qualitative study on patients and doctors. BMC Fam Pract. 2014;15:67. doi: 10.1186/1471-2296-15-67. PubMed PMID: 24739595; PMCID: PMC3996170.
50. Laue J, Melbye H, Halvorsen PA, Andreeva EA, Godycki-Cwirko M, Wollny A, Francis NA, Spigt M, Kung K, Risor MB. How do general practitioners implement decision-making regarding COPD patients with exacerbations? An international focus group study. International journal of chronic obstructive pulmonary disease. 2016;11:3109-19. doi: 10.2147/COPD.S118856. PubMed PMID: 27994450; PMCID: PMC5153277.
51. Davies F, Risor MB, Melbye H, Spigt M, Brookes-Howell L, O'Neill C, Godycki-Cwirko M, Wollny A, Andreeva E, Butler C, Francis N. Primary and secondary care clinicians' views on self-treatment of COPD exacerbations: a multinational qualitative study. Patient education and counseling. 2014;96(2):256-63. doi: 10.1016/j.pec.2014.05.011. PubMed PMID: 24910421.
52. Aggarwal NK, Cedeno K, Guarnaccia P, Kleinman A, Lewis-Fernandez R. The meanings of cultural competence in mental health: an exploratory focus group study with patients, clinicians, and administrators. Springerplus. 2016;5:384. doi: 10.1186/s40064-016-2037-4. PubMed PMID: 27065092; PMCID: PMC4814393.
53. Zeitz HJ. Problem based learning: development of a new strategy for effective continuing medical education. Allergy Asthma Proc. 1999;20(5):317-21. PubMed PMID: 10566102.
54. Onyon C. Problem-based learning: a review of the educational and psychological theory. Clin Teach. 2012;9(1):22-6. doi: 10.1111/j.1743-498X.2011.00501.x. PubMed PMID: 22225888.
55. Azer SA, Peterson R, Guerrero AP, Edgren G. Twelve tips for constructing problem-based learning cases. Med Teach. 2012;34(5):361-7. doi: 10.3109/0142159X.2011.613500. PubMed PMID: 22452277.
56. Idowu Y, Muir E, Easton G. Problem-based learning case writing by students based on early years clinical attachments: a focus group evaluation. J R Soc Med Open. 2016;7(3):2054270415622776. doi: 10.1177/2054270415622776. PubMed PMID: 26981255; PMCID: PMC4776248.

57. Chan ZC. Exploring creativity and critical thinking in traditional and innovative problem-based learning groups. *J Clin Nurs.* 2013;22(15-16):2298-307. doi: 10.1111/jocn.12186. PubMed PMID: 23452036.
58. Case-based Teaching and Problem-based Learning.: Center for Research on Learning and Teaching. Available from: <http://www.crlt.umich.edu/tstrategies/tscbt>.
59. Rubin DB. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons; 1987.